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NITSBIN

1ST EDITION

BEDSIDE ORIENTED INTERNAL MEDICINE

> “Medicine is not only a Science; it is also an art”
>
> Paracelsus

AUTHOR

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FOR MEDICAL, HEALTH SCIENCE STUDENTS AND JUNIOR PRACTITIONERS IN ETHIOPIA

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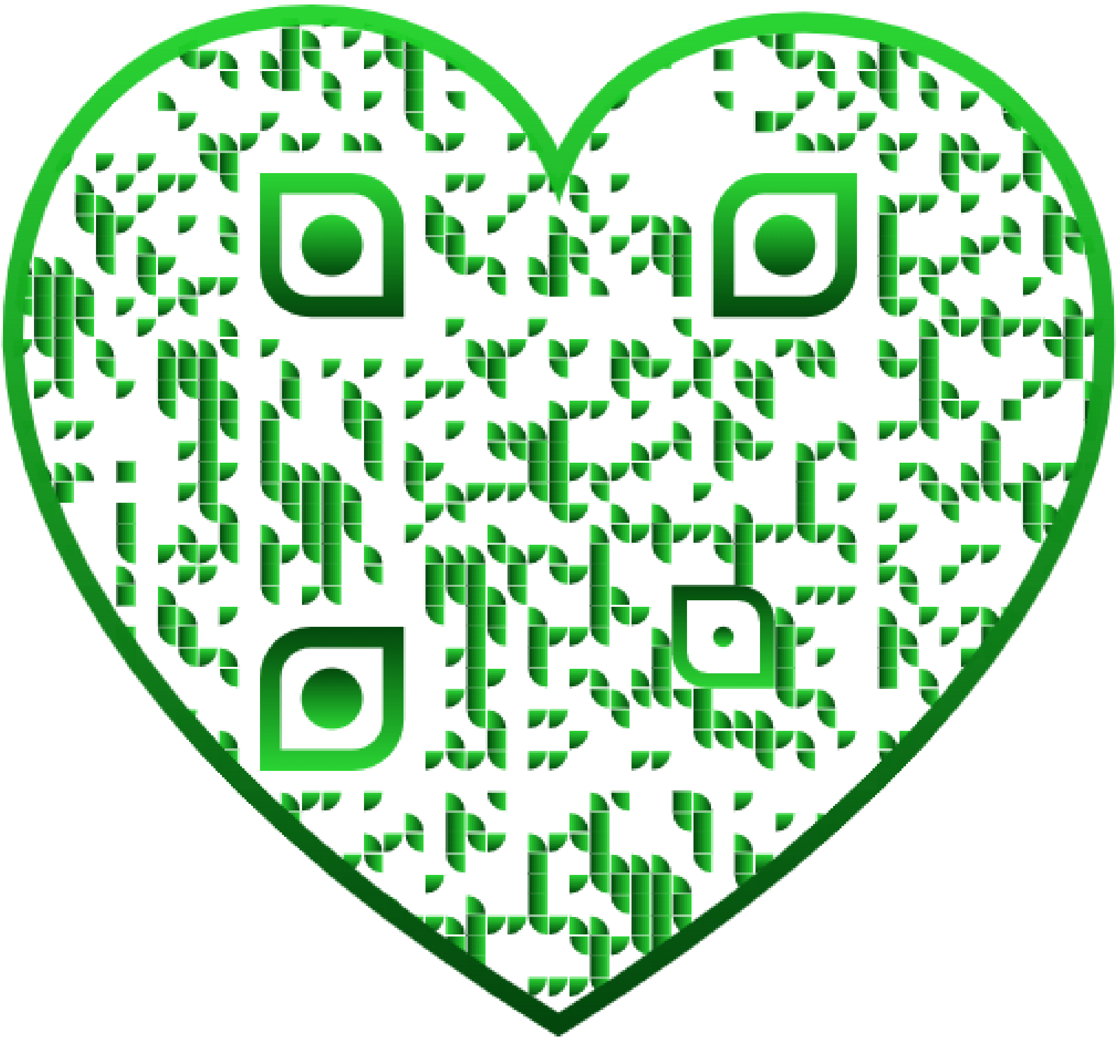

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Commemoration

This book is in memory of **Dr. Habtamu Animaw,** who lost his life suddenly, due to unknown cause, two months before his graduation, in paqume 03, 2012 E.C, while working his internship ward activity, at University of Gondar Hospital.
May his soul Rest in peace.

"Medicine is not only a science, but also an art!"
(ሕክምና ሳይንስ ብቻ ሳይሆን ጥበብም ነው!)

"Your single comment is constructive for the next revised edition"

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ለኢትዮጵያ
1st edition
Nitsibin(ንጽቢን)
Internal medicine

Preface

Nitsbin means “Book of art” in Geez language (ንጽቢን በልሳነ ግእዝ “የጥበብ መጽሐፍ” ማለት ነው ። ሐኪም ማለትም ሐከመ = ጥበበኛ ሆነ ፣ ብልሃተኛ ሆነ ከሚለው የግእዝ ግስ ተገኝቷል ። ሐኪም ማለት ጥበበኛ ከሆነ፤ ሕክምና ማለት ደግሞ ጥበብ ይሆናልና ይህን ቃል ወደድን). We also prefer this name because **“Medicine is not only a Science; it is also an art”** as said by Paracelsus. So, **Nitsbin means** “**book of medicine**” **indirectly.**

The book is made on common Medical cases & approaches by Ethiopian Junior medical doctors (GP) to be used as a quick reference & guide. The aim of Nitsbin is to enable & equip medical students with the basic & necessary medical knowledge, skills & approaches to patients in a very short period of time. We hope that, it will be important also for junior medical and health science practitioners.

Nitsbin is a modified form of my previous bedside note **“Internal medicine long and short case notes by Mulualem.G (ኦሪት)”** which was prepared in 2010 E.C during my 4th year (C-I) attachment. I was considering only for myself and it was in hand written form. But I found that most of students need a short-revised note for Clinical case approach and it was necessary to revise the hand written note in to short and precise book with the intension of collecting & comprising common medical cases in one place for easy access for undergraduates and junior medical and health science practitioners.
We recommend you to read Standard books first and use Nitsbin as revision. Otherwise depending only on Nitsbin is strongly forbidden.

Nitsbin has two major parts; long cases (containing 14 chapters and case report sample) & short cases (containing 11 chapters).
Long cases contain important information on how to approach patients. Like;

- ✓ Some basic Information for taking history (clinical features, cause and risk factors, complications, DDx…)
- ✓ Pertinent physical examination findings
- ✓ Sample histories for each case
- ✓ Investigations to be done & what is expected from each investigation considering availability in Ethiopia and cost effectiveness.
- ✓ Discussion about the case & management
- ✓ Case reporting format for bedside, round, exam and case discussion

Short cases mainly contain

- ✓ Exam oriented physical examination techniques and possible findings
- ✓ DDX, IX and management principles of common physical examination findings
- ✓ Common medical procedures with indication, contraindication, complication of a procedure, principle of management and result analysis with YouTube video link for each procedure.
- ✓ Emergency and OPD cases
- ✓ Poisoning, Drug Overdose, and Envenomation
- ✓ CXR Interpretation
- ✓ Basics of ECG and ECG interpretation
- ✓ Basics about rational use of antibiotics
- ✓ Symptoms and signs in Amharic (የበሽታ ምልክቶች አማርኛ ትርጉም)
- ✓ Anatomical body parts in Amharic (የሰውነት አካል ክፍሎች አማርኛ ትርጉም)
- ✓ Common Laboratory Investigations with practical points and procedures (plus you tube video link)
- ✓ Reference Intervals for Laboratory Tests

Acknowledgment

I thank God first and most for everything that had been and that ever will be, it is all by the will of God.

I would like to acknowledge **Dr. Asmare Walle and Dr. Robel Dibaba (Co-Author's)** for their contribution in the preparation of this Bedside oriented book. If it was not for you, I know this book will never been real. Lastly with effortful contribution of co-authors, we prepared Nitsbin as a ''Bedside oriented book'' depending on our clinical year attachment experiences.

My Special thanks is owed to **Mr. Getahun wedaje (Medical laboratory technologist)** for sharing files and for your comments on Chapter 10; Common Laboratory Investigations with practical points and procedures. I also thank **Mr. Yimesgen Gashaw** who design medical logo of *"Nitsbin Internal medicine, ንጽቢን የውስጥ ደዌ ሕክምና"*

I would also like to thank **my juniors and classmates at UOG** who was using my hand note *(orit Internal medicine long and short case notes)* and providing me constructive comments. They also initiated me to prepare the hand written form into a short and precise revision book. So, this book come to reality.

Lastly, I would also like to acknowledge the cover page designer Mr. Tadele Tesfaye (Phone number: +251 91 881 2871. Email: tadeletesfaye600@gmail.com. Telegram: https://t.me/Tadele_tesfaye)

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Acronyms & Abbreviations

✓ +ve… positive
✓ -ve… negative
✓ 2ry… Secondary
✓ a.k.a…. Also known as
✓ AAA… abdominal aortic aneurism
✓ ABG… arterial blood gases
✓ ACE-I… angiotensin converting enzyme inhibitors
✓ ADA… Adenosine deaminase
✓ AF…. Atrial fibrillation
✓ AFI… Acute febrile illness
✓ AI… Apical impulse
✓ AKI…. Acute kidney injury
✓ ARB's… Angiotensin- II receptor Blockers (RAAS blocking agents)
✓ ARDS…. adult respiratory distress syndrome
✓ ARF… Acute rheumatic fever
✓ ASA… acetyl salicylic acid (Aspirin)
✓ ASAP…As soon as possible
✓ ASD… Atrial septal defect
✓ ASL… acutely sick looking
✓ ASO… anti streptolysin O
✓ Ass't…. Assessment
✓ AVM… Arteriovenous malformations
✓ BAL… Broncho alveolar lavage
✓ BF… Blood film
✓ BID… two times per day, every 12 hr (lat. bis in die)
✓ BM… Bone marrow
✓ BNP… Brain natriuretic peptide
✓ BSS… Brown Sequard syndrome
✓ BUN… blood urea nitrogen
✓ C.C… chief compliant
✓ C/F… Clinical feature
✓ CBC… complete blood cell count
✓ CCB's… Calcium channel blockers
✓ CF… Cystic fibrosis
✓ CHD…. Congenital heart Disease
✓ CHF…. Congestive heart failure
✓ CKD…. Chronic kidney disease
✓ CLD… Chronic liver disease
✓ CLL… Chronic lymphocytic leukaemia
✓ CML… Chronic myelogenous leukaemia
✓ CMP…Cardiomyopathy
✓ Cmn … Common
✓ CN… Cranial nerve
✓ CNS… Central Nervous system
✓ CO…cardiac out put
✓ JVP…jugular venous pressure
✓ LABA … long acting β2-agonists
✓ LAP… Lymphadenopathy
✓ LBBB… Left bundle branch block
✓ LDH… Lactate dehydrogenase
✓ LDL… Low density lipoprotein
✓ LFT… liver function test
✓ LGS… Lymphoglandular system
✓ LL… lower limb
✓ LLSB… left lower sternal border
✓ LMNL… Lower motor neuron lesion
✓ LMWH… Low molecular weight heparin
✓ LOC…Loss of consciousness
✓ LP… Lumbar puncture
✓ LSHF … left sided heart failure
✓ LVH… left ventricular hypertrophy
✓ MCL… mid clavicular line
✓ MDI… metered dose inhaler
✓ Mgt…management
✓ M. HCT… Manual hematocrit
✓ MI… myocardial infarction
✓ MND… Motor neuron disease
✓ MRSA… Methicillin resistant staph aureus
✓ MS… Multiple sclerosis
✓ MSP… Multiple sexual partner
✓ MSS… Musculoskeletal system
✓ MSSA… Methicillin sensitive staph aureus
✓ NHL… No Hodgkin lymphoma
✓ NIS… Non icteric sclera
✓ NR…. Non-reactive
✓ NS… Nervous system
✓ NSAID's… Non-steroidal anti-inflammatory drugs
✓ OCS … oral corticosteroid
✓ OGTT… oral glucose tolerance test
✓ OI… opportunistic infection
✓ P/E… physical examination
✓ PC… Pink conjunctiva
✓ PCKD… polycystic kidney disease
✓ PCV… polycythaemia vera
✓ PDA… Patent Ductus arteriosus
✓ PE… pulmonary embolism
✓ PICT… Provider initiated counselling and testing (currently changed to PITC)
✓ PKDL… post kalazar dermal leishmaniasis
✓ PLE… Protein losing enteropathy
✓ PM/PB… Peripheral morphology/ peripheral blood smear

- ✓ COPD…chronic obstructive Pulmonary disease
- ✓ CRMVHD… chronic rheumatic multi valvular heart disease
- ✓ CSF… Cerebrospinal fluid
- ✓ CSL… chronically sick looking
- ✓ CT… computed tomography
- ✓ CVS… Cardiovascular system
- ✓ CXN… complications
- ✓ CXR… chest X-ray (chest radiography)
- ✓ DBP… diastolic blood pressure
- ✓ DDX…. differential diagnosis
- ✓ DIC… Disseminated intravascular coagulation
- ✓ DM… Diabetic Mellitus
- ✓ DRE… Digital rectal examination
- ✓ DTR…Deep tender reflex
- ✓ DVHD… degenerative valvular Heart Disease
- ✓ DVT… deep vein thrombosis
- ✓ Dx …. Diagnosis
- ✓ EBV… Epstein-barr virus
- ✓ ECG…. Electrocardiography
- ✓ Echo… echocardiography
- ✓ ED… Emergency department
- ✓ EDS… Ehlers-Danlos syndrome
- ✓ ESRD…. End stage renal disease
- ✓ FBS… Fasting blood sugar level
- ✓ FND… Focal neurologic deficit
- ✓ FSGS… Focal segmental glomerulosclerosis
- ✓ GBS… Generalized body swelling
- ✓ GBS… Guillain barre syndrome
- ✓ GCS… Glasgow coma scale
- ✓ GCS… Glucocorticosteroid
- ✓ GUS… Genitourinary system
- ✓ HAART / ART… Highly active antiretroviral therapy / antiretroviral therapy
- ✓ HBA1c… glycosylated haemoglobin
- ✓ HCC… Hepatocellular carcinoma
- ✓ HCMP… Hypertrophic cardiomyopathy
- ✓ HDL… High density lipoprotein
- ✓ HEENT… Heed, ears, eyes, nose and throat
- ✓ HF… Heart Failure
- ✓ Hgb… Haemoglobin
- ✓ HGIF… High grade intermittent fever
- ✓ HHD…hypertensive Heart Disease
- ✓ HL… Hodgkin lymphoma
- ✓ HMS… Hyperactive malarial splenomegaly
- ✓ HPI… history of present illness
- ✓ HRCT… high resolution computed tomography
- ✓ HSS… Hepatosplenic schistosomiasis
- ✓ HSV… Herpes simplex virus
- ✓ HTN… hypertension
- ✓ Hx… history
- ✓ PND… paroxysmal nocturnal dyspnoea
- ✓ PO… by mouth (lat. Per Os)
- ✓ PRN… Per need or as needed
- ✓ Pt…. Patient
- ✓ PTE… pulmonary thromboembolism
- ✓ QD… daily, once per day (lat. Quaque in die)
- ✓ QID… four times per day, every 6 hr (lat. quarter in die)
- ✓ r/o… rule out
- ✓ RAAS… Renin Angiotensin aldosterone system
- ✓ RBBB… Right bundle branch block
- ✓ RBS… random blood sugar level
- ✓ RES… Reticuloendothelial system
- ✓ RF… risk factor
- ✓ RFT… Renal function test
- ✓ RHD…. Rheumatic heart Disease
- ✓ RS… Respiratory system
- ✓ RSHF … Right sided heart failure
- ✓ RSHF… right sided heart failure
- ✓ RV … right ventricle (right ventricular)
- ✓ RVHD… Rheumatic valvular Heart Disease
- ✓ SABA… Short acting β2-agonists
- ✓ SAH… Subarachnoid haemorrhage
- ✓ SaO_2/SO_2/SPO_2… Saturation of oxygen
- ✓ SBP... systolic blood pressure / spontaneous bacterial peritonitis
- ✓ SCC… Squamous cell carcinoma
- ✓ SCD… sudden cardiac death
- ✓ SDH… subdural haematoma
- ✓ SLE… systemic lupus erythematosus
- ✓ SOB…. Shortness of breath
- ✓ Ssx… Syndrome
- ✓ TB… Tuberculosis
- ✓ TFT… Thyroid function test
- ✓ TGA … transposition of great arteries
- ✓ TIA … transient ischaemic attack
- ✓ TID… three times per day, every 8 hr (lat. ter in die)
- ✓ TM… transverse myelitis
- ✓ TTP… Thrombotic thrombocytopenic purpura
- ✓ TVLS… Total vertical liver span
- ✓ U/A… Urine analysis
- ✓ U/L… Unit per litre
- ✓ U/S… Ultrasound
- ✓ UL… Upper limb
- ✓ UMNL… Upper motor neuron lesion
- ✓ UOP… Urine out put
- ✓ VHD… Valvular Heart Disease
- ✓ VL… Visceral leishmaniasis
- ✓ VTE… Venous thromboembolism

- ✓ HZV… Herpes zoster virus
- ✓ ICH … Intra cranial hemorrhage
- ✓ ICP… Intracranial pressure
- ✓ ICS … Inter costal space/ inhalational corticosteroid
- ✓ IDA… Iron deficiency anaemia
- ✓ IDSA… Infectious disease society of America
- ✓ IE… infective endocarditis
- ✓ IHD… Ischemic heart disease
- ✓ ILD…Interstitial lung disease
- ✓ IM… intra muscular injection
- ✓ IM… Infectious mononucleosis
- ✓ IP… Incubation period
- ✓ IPF… Idiopathic pulmonary fibrosis
- ✓ IRIS… Immune reconstitute inflammatory syndrome
- ✓ IS… Integumentary system
- ✓ IU… International unit
- ✓ IV… intravenous injection

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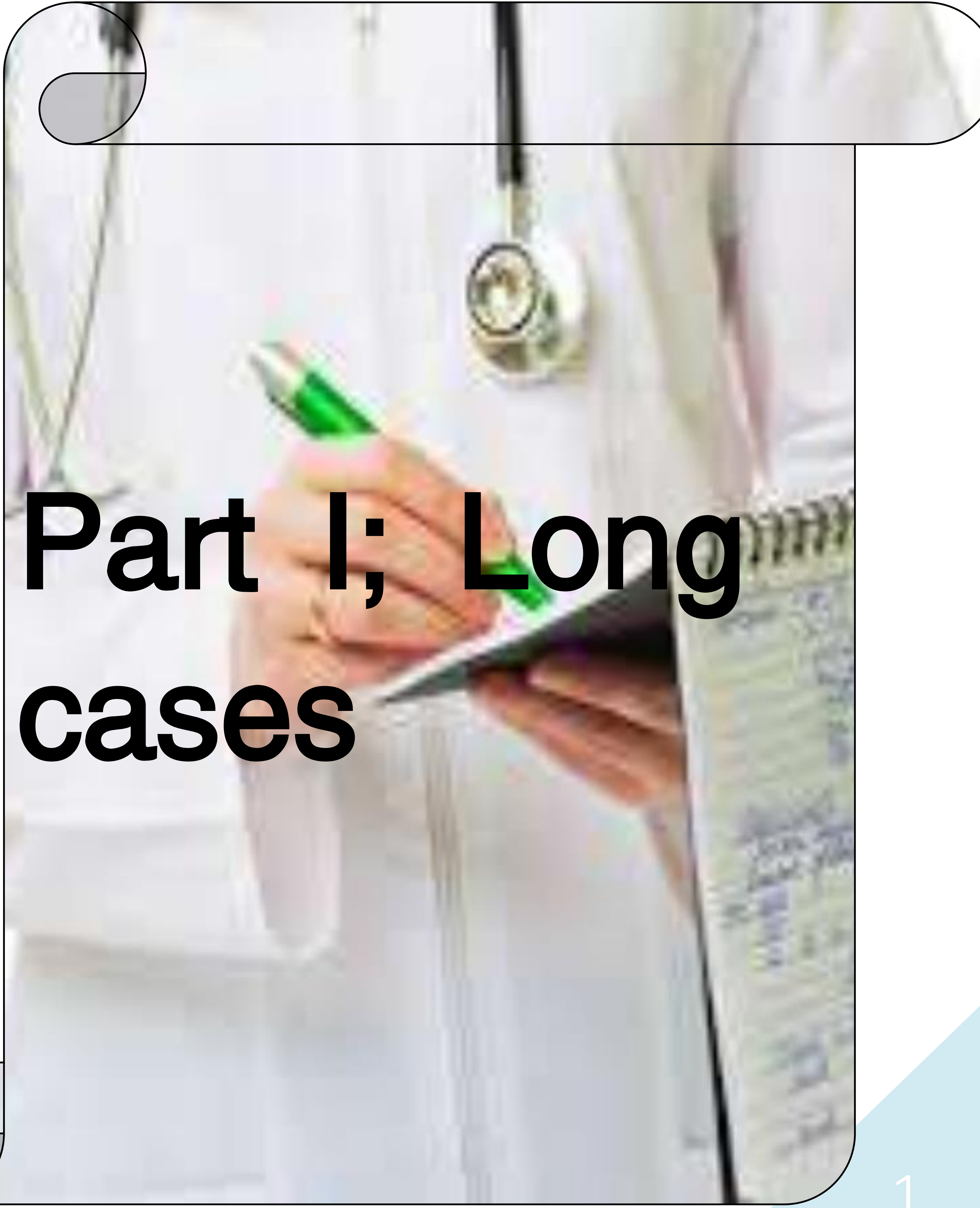


Part I; Long cases

Mysteries of best physician's about patient approach

especially for bedside, round and Oral exam presentation

- History → even though, there is interpersonal variations most experts prefer the following way of history preparation
    - elaborate the chief compliant including aggravating and relieving factors followed by associated symptoms.
    - For chronic patients firstly explain the chronic condition then elaborate the current condition which leads you what was going on progressively. Don't forget Adherence and follow up. For example, the precipitant for DKA may be drug discontinuation and follow up at chronic OPD is one part of management for chronic diseases.
    - Then write positive and negative statements. Pertinent negative statements have almost equal importance as pertinent positive statements (e.g. if you say there is no history of Alcohol intake for CLD patient, you are almost excluding alcoholic liver disease)
    - The order of +ve and -ve statements should be risk factor and precipitants, then complication, last but not the least DDX. But, if there is pertinent positive, put as top before pertinent negatives regardless of being RF, CXN or DDX. Always list in the order from most common to least common and consider geographic area of the patient (for example for meningitis patient from low land area, you have to consider cerebral malaria as a DDX)
- Put pertinent physical examination findings and don't miss pertinent negatives
- Write your diagnosis and make it complete (e.g NYHA class IV, stage C, CHF 2ry to CRMVHD (MR, TR, AR) precipitated by CAP)
    - After putting your full DX, write your evidence for the case (You have to convince by the the order of pt's smx, sign, other supportive evidence, RF ± Ix findings. 1st put your +ve evidence then add -ve evidences)
- List your differential diagnosis in the order from most common to least common (and consider what is common in our setup rather than those written based on western setup).
    - While you are listing DDX you have to know what is in favor and against for that specific DDX. It is better not to list DDX that you don't explain well. The examiner will ask you based on what you are telling him/her.
- List IX (better if you list baseline IX, diagnostic IX and common ones first followed by supportive IX, IX for mgt purpose and drug toxicity, finally follow up IX. for clinical practice, consider those available in Ethiopia and patients' affordability)
- Last but not list is management principle of your case (Diagnosis).

GOOD LUCK!!!

Chapter 1; Heart failure (ልብ ድካም)

Dr. Mulualem. G

Clinical features and how to write hx of cardiac patient

History

- **The cardinal symptoms of heart failure (HF) are fatigue and shortness of breath.**
- **Fatigue**
  - Although fatigue traditionally has been ascribed to the low cardiac output in HF, it is likely that skeletal-muscle abnormalities and other noncardiac comorbidities (e.g., anemia) also contribute to this symptom.
  - Fatigue is a non-specific symptom: if the predominate symptom is fatigue consider also Hypothyroidism, Adrenal insufficiency, CKD, CLD, DM and after exclusion of organic causes: chronic fatigue syndrome.
- **Dyspnea or shortness of breath** → Defined as difficult or labored breath
  - **In the early stages of HF, dyspnea is observed only during exertion; however, as the disease progresses, dyspnea occurs with less strenuous activity, and it ultimately may occur even at rest.**
  - The origin of dyspnea in HF is probably multifactorial.
  - The most important mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxta capillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea.
  - Other factors that contribute to dyspnea on exertion include reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue, and anemia.
  - Dyspnea may become less frequent with the onset of right ventricular (RV) failure and tricuspid regurgitation
- **Orthopnea**
  - Defined as **dyspnea occurring in the recumbent position**
  - It is usually a later manifestation of HF than is exertional dyspnea.
  - It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure.
  - Orthopnea generally is **relieved by sitting upright or sleeping with additional pillows.**
  - Although orthopnea is **a relatively specific symptom of HF**, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture
- **Nocturnal cough**

  - It is a common manifestation of the process seen in orthopnea and a frequently overlooked symptom of HF.
  - Most Commonly **position dependent productive nocturnal cough with whitish frothy sputum**
- **PND** (Paroxysmal nocturnal dyspnea)
  - This term refers to acute episodes of **severe shortness of breath and coughing that generally occur at night and awaken the patient from sleep**, usually 1 - 3 h after the patient retires.
  - PND may manifest as coughing or wheezing, possibly because of increased pressure in the bronchial arteries leading to airway compression, along with interstitial pulmonary edema that leads to increased airway resistance.
  - Whereas orthopnea may be relieved by sitting upright at the side of the bed with the legs in a dependent position, **patients with PND often have persistent coughing and wheezing even after they have assumed the upright position.**
- **Palpitations**
  - An unexpected awareness of the heartbeat.
- **Cardiac asthma**
  - It is closely related to PND, is characterized by wheezing secondary to bronchospasm, and must be differentiated from primary asthma and pulmonary causes of wheezing.
- **Ankle swelling if patient develop Congestion (i.e. CHF)**
  - **It is a cardinal manifestation of CHF**
  - **Ankle edema of cardiac origin is usually symmetrical and worst in the evenings, with improvement during the night. (if the patients spend a lot of time lying down, we may see sacral edema)**
  - As failure progresses, edema ascends to involve the legs, thighs, genitalia and abdomen (i.e. progressive edema to become GBS).
  - Also gain in weight of ≥ 3 kg
  - **Remark:** generalized edema is by definition fluid accumulation at intestinal space (soft tissue) along with third space (plural, peritoneal and pericardial)
  - See Peripheral pitting edema from physical examination in HF below
- **Weight loss (Cardiac cachexia)**
  - With severe chronic HF, there may be marked weight loss and cachexia.
  - Significant weight loss when pt loss ≥ 10% of his/her initial body weight within 6 months
  - Although the mechanism of cachexia is not entirely understood, it is probably multifactorial (may be, due to anorexia from hepatic and intestinal congestion or mesenteric hypoxia).
  - When present, cachexia augurs a poor overall prognosis.
- **Chest pain**
  - May be from angina (in MI), Pericarditis or from precipitants like Pneumonia, PTE etc.
- **Other Symptoms**

- Patients with HF also may present with **GI symptoms**;
    - **Anorexia, nausea, and early satiety** associated with **abdominal pain and fullness** are common complaints and may be related to edema of the bowel wall and/or a congested liver.
    - Congestion of the liver and stretching of its capsule may lead to **right upper quadrant pain.**
- **Cerebral symptoms** such as **confusion, disorientation, and sleep and mood disturbances** may be observed in patients with severe HF, particularly elderly patients with cerebral arteriosclerosis and reduced cerebral perfusion.
- **Nocturia** is common in HF and may contribute to insomnia. (Bed rest will increase renal blood flow as do urine output)
- **Syncope, presyncope and dizziness**
    - CNS manifestations due to decreased cardiac output
    - Syncope*:* a transient loss of consciousness. There are different circumstances in which the syncope occurs such as;
        - Postural syncope: on standing for prolonged periods or standing up suddenly
        - Micturition syncope: while passing urine
        - Tussive syncope: on coughing or
        - Vasovagal syncope: with sudden emotional stress
        - **Remark;** cardiac vs vasovagal syncope
            - Cardiac syncope has no previous syncopal episodes. But syncope happens during activity or at peak activity, there is family Hx of heart disease, and usually with abnormal ECG. In contrast to cardiac syncope, vasovagal will have presyncope episodes, syncope trigger, prolonged standing and lightheadedness symptom.
    - Presyncope: a transient sensation of weakness without loss of consciousness.
    - Dizziness → feeling of light headedness

Characterization of patient history

- **Pt's may present with**
    - SOB… most common presentation
    - GBS
    - Bilateral leg swelling
- **If a known cardiac patient** → ask the following on your hx
    - For how long he/she was Diagnosed to have cardiac disease
        - e.g a known cardiac pt for the past 5 years or you can say 5 years back he/she was told to have cardiac disease (you can ask what was the presentation at that time and how Dx was made… no need to write on your HPI)

  - What medication he/she was taking… e.g he/she was on Lasix(furosemide), spironolactone, benzathine penicillin ... ask dose and frequency of each drug
    - Dietary modification like on salt free diet, recommended to decrease alcohol intake and to avoid smoking.
  - Adherent or not
  - Where was the follow up and frequency (every month, every two months….)
  - How was his/her smx's in between… improving, worsening or no change at all… if not improving or worsening what was the reason (non-adherence, wrong diagnoses…)
- SOB (dyspnea)
  - Insidious in onset
  - Progressively worsening (e.g he/she experienced Dyspnea while doing supra ordinary activities like…. Followed by dyspnea while doing sub ordinary activities like… and later dyspnoea at rest… when was the time for each)
- Orthopnea… how many pillows he/she use during bed time (e.g orthopnea of 3 pillows)
- PND…. Pt awake from sleep and open windows for Air hunger
- Palpitation
- Cough
  - Most Commonly **position dependent productive nocturnal cough with whitish frothy sputum** (even though this is the typical character of cough in HF, it can be bloody or even Hemoptysis in some cases like patient with MS, pulmonary edema or PTE)
  - It can be dry and persistent then become productive
    - Position dependent (aggregated when he/she assume supine position)
    - Whitish and frothy
    - Non foul smelling
    - Non blood tingled
    - Quantify the amount… e.g 3-4 Arabic coffee cup per day
- Leg swelling … ask the following
  - Symmetry → bilateral or unilateral (most commonly bilateral. Unilateral swelling in CHF is less likely)
  - Site → pedal, swelling up to the knee, GBS
  - Duration
  - Progression… e.g goes upwards starting from knee within 2 weeks duration
  - Diurnal variation → disappear in the morning and marked on sitting position or prolonged standing
  - How the pt noticed the swelling
  - Painful or not …. Mostly painless

N.B body swelling

- **In cardic pt. →start from leg and goes upward**
- **In renal disease → begin from face (morning facial puffines)**
- **In liver disease → start with abdominal distension which may progress to GBS**

- Weight loss
    - E.g. significant weight loss from 53 kg to 45 kg which is 15% of his/her initial body weight or
    - Unquantified but significant weight loss to the extent his/her closes become loose (if s/he didn't remember his/her initial body weight but claim that S/he lose his/her body weight)
    - Make sure that the patient is not in diuretics
- Chest pain → angina (common in old age → M ≥ 45 years, F ≥ 55 years)
    - Retro sternal chest pain
    - Squeezing type, heaviness, pressure/burning sensation
    - Radiates to left shoulder or medial border of left arm (it can radiate from jaw to umbilicus)
    - Worsened by exertion and relieved by rest or taking nitroglycerine (nitrates)
    - Lasts for 2-5 minutes
    - Levine sign +ve… pt make a fist and put his fist on chest to characterize the smx
    - **Remark:** nitroglycerine alleviate chest pain because of esophageal spasm
- Wheezing…. Diffuse due to cardiac asthma

Preciptant factors

Remember with the mnemonics "HEART FAILES"

- HTN
- Endocarditis (IE)
- Arrhythmia (manifest with new onset palpitation and Irregularly irregular pulse)
- Recurrent rheumatic fever and myocarditis
- Thyrotoxicosis and pregnancy
- Fever (for infection)
- Anemia
- Infarction
- Lung infection (e.g. pneumonia)
- Embolism (PE, DVT)
- Stress (Dietary i.e. Salt intake, Drug withdrawal, Psychological stress, physical stress)

Other Risk factors to be assessed in cardiac pt.

- Alcohol drinking, chat chewing, cigarette smoking (Smoking, Alcohol, chat and DM fasten atherosclerotic before the age of 45 which may end up in IHD and also RF for HTN)
- Family hx of sudden cardiac death → associated with HCMP (most commonly in athletes) and MI
- Family hx of similar illness→ DCMP

- DM…associated with metabolic sxx (HTN, DM, Hyperlipidaemia, Central obesity)

Complication of CHF

- Severe CHF→ progression of natural course of the diseases resulting in death
- **AKI**→ resulting from pre renal azotemia (Cardio-renal syndrome)
- **Cardio embolic stroke**
- Pulmonary hypertension
- Cardiac cirrhosis → which may lead to all complication of cirrhosis like Hepatic encephalopathy, esophageal varices and others
- Cardiac cachexia
- Endocarditis and Arrhythmia (atrial Fibrillation)
- ? Anemia of chronic illness (NEW NAME: Anemia of inflammation)
- Fluid and electrolyte disturbances
    - Hypocalcemia, hypomagnesemia, hypokalemia, hyponatremia

Sample history one

Sample hx of a pt' from chilga with a DX of NYHA class IV, stage III CHF 2ry to CRMVHD (MR, TR and AR) precipitated by CAP.

Chief compliant

SOB of three months duration

HPI

This patient was last relatively healthy 3 months back, at which time she started to experience a gradual onset of dyspnea while doing ordinary activities like going to church which progressively increase in severity and she began to experience shortness of breath at rest within one month. Associated with orthopnea of 3 pillows, PND and Palpitation.

One month before admission, she started to experience a gradual onset of dry cough which later becomes position dependent productive nocturnal cough with whitish and frothy, non-foul smelling, Non blood tingled, sputum of 3-4 Arabic coffee cup per day which is aggregated when she assumes supine position but no chest pain or fever.

Concomitantly she also experienced bilateral, painless leg swelling which starts from foot and goes upwards to involve the whole leg within 2 weeks duration. The swelling disappears in the morning and marked on sitting position or prolonged standing.

She has also significant weight loss from 40 kg to 35 kg within 3 months which is 12.5% of her initial body weight.

Two weeks before admission she experienced chest pain, fever, fast breathing and worsening of cough for which she visited a local health center at chillga where she was given augmentin 625 mg, PO,TID for 7 days and azithromycin 500mg, po, daily for 3 days (hx from referral paper) but no improvement. Later she was referred to our hospital for better investigation and mgt.

- No hx of Fever, reddish discoloration of urine(haematuria), dental manipulation (tooth extraction), GI/GU manipulation, IV drug abuse or intra cardiac device (IE)
- She doesn't remember hx of sore throat, migratory joint pain, swelling over joints, or abnormal body movement (Rheumatic fever)
- No hx of Anterior neck swelling, heat intolerance, profuse sweating, sleep disturbance, palpitation, tremor or irritability *(thyrotoxicosis)*
- No Hx of chest pain or intermittent claudication (Atherosclerosis: MI or PAD)
- She was screened for RVI 6 months back and found to be NR *(RVI is RF for DCMP)*
- No hx of chronic cough, contact with chronic cougher or a known TB pt, no hx of previous TB RX *(TB is common cause of constrictive pericarditis and chest infection can precipitate CHF)*
- No hx of cigarette smoking, chronic alcohol intake or chewing chat *(Smoking, Alcohol, chat and DM fasten atherosclerotic before the age of 45 which may end up in IHD. And also, RF for HTN)*
- No hx of Drug intake (Common drugs like NSAID are also a risk factor for MI, Digoxin is risk factor for Atrial fibrillation, Doxorubicin and Cocaine result in DCMP)
- No hx of easy fatigability, blurring of vision, light headedness, tinnitus or vertigo.
- She usually eats injera made of "teff" and "machilla" and "wott" made of "atter" and "dagusa" 3-4 times per day. Occasionally he/she eats meat during holidays *(salt is precipitant of CHF, Vitamin B1 deficiency/wet beriberi/ can result in DCMP, Hemochromatosis also RF for DCMP)*
- No hx of Flank pain, facial puffiness reduced urine output. *(CKD… DDX for GBS, Cardio renal Sxx)*
- No hx of RUQ abdominal pain, yellowish discoloration of eyes, pale stool or dark urine *(CLD as DDX)*
- No self or family hx of HTN, DM or asthma *(RF)*

Finally, she was admitted to our hospital carried on stretcher by her families

➡ **N.B these +ve and -ve statements may not be included in all causes of CHF. So, modify based on your case**

Sample history two

Sample hx of a pt' from koladiba with a DX of NYHA class IV stage C CHF 2ry to RHD Preciptated by drug discontinuation

Chief compliant

Generalized body swelling and exacerbation of SOB of a week duration

HPI

This is a known cardiac pt for the past 5 years on enalapril to be taken 1 tablet twice per day and Lasix (furosemide) to be taken half tablet two times per day, on salt free diet and recommended to decrease alcohol intake and to avoid smoking. He was on follow up every month here in our hospital. He discontinued his medication 4 months back due to financial problem.

A week before admission, he started to experience exacerbation of shortness of breath at rest associated with orthopnea of 4 pillows, PND, Palpitation, easy fatigability and generalized body swelling which starts from foot and goes upwards to involve the leg, abdomen and finally the face within a week. He has also unquantified but significant weight loss to the extent his closes become loose.

Associated with this he has also position dependent productive nocturnal cough of whitish and frothy, non-foul smelling, Non blood tingled sputum of 1ACC/day which is aggregated by lying supine position.

Two months back he developed dyspnea at sub-ordinary activities like going to toilet, Orthopnea of two pillows, PND and position dependent dry cough. For this he was admitted at UOGH for two weeks and discharged improved and appointed with the above medications at cardiac clinic.

Physical examination (pertinent findings)

Readers are recommended to see CVS examination from short case of Nitsbin (click here → 1.2 Cardiovascular System)

1 GA

- ✓ Patient may be Acute sick looking, chronic sick looking or acute sick looking on chronic background depending on the underlying cause and presence of complication
- ✓ May be in cardio-pulmonary distress (click and see 1.2 Cardiovascular System examination)
- ✓ **In mild or moderately severe HF,** the patient appears to be in **no distress at rest** except for feeling uncomfortable when lying flat for more than a few minutes.
- ✓ In more severe HF, the patient must **sit upright, may have labored breathing, and may not be able to finish a sentence** because of shortness of breath.

2 Vital signs

- ✓ BP

    - SBP may be normal or high in early HF, but it generally is reduced in advanced HF because of severe LV dysfunction.
    - The pulse pressure may be diminished, reflecting a reduction in stroke volume.
    - If there is HTN it may be a cause of CHF or 2ry HTN from CHF
    - **Remark:** the presence of left sided S3 gallop may tell us long standing HTN may be the cause of CHF.
    - OHT → from Anemia, diuretics etc.
    - Wide pulse pressure → AR, Anemia, thyrotoxicosis, pregnancy
    - Narrow pulse pressure → AS, Blood loss, cardiac tamponade.
- ✓ PR
    - Sinus tachycardia is a nonspecific sign caused by increased adrenergic activity as a compensatory mechanism for low output failure
    - Tachycardia is minor criteria of Framingham criteria
    - Week pulse → Shock, AS
    - Irregularly irregular pulse → AF (precipitant or 2ry cause of CHF), multifocal atrial tachycardia.
    - Pulses alterans → Rare finding from Advanced CHF
- ✓ Temperature
    - Febrile → Can be from IE, Pneumonia or other infections, Rheumatic fever (rare in adults to present with rheumatic fever but common in children)
    - Hypothermia → low CO stat (Cardiogenic shock or sepsis)
- ✓ RR
    - Cheyne-Stokes Respiration
        - Also referred to as periodic respiration or cyclic respiration
        - Present in 40% of patients with advanced HF and usually is associated with low cardiac output.
        - It is caused by an increased sensitivity of the respiratory center to arterial Pco2 and a lengthy circulatory time.
        - There is an apneic phase, during which arterial PO_2 falls and arterial PCO_2 rises.
        - These changes in the arterial blood gas content stimulate the respiratory center, resulting in hyperventilation and hypocapnia, followed by recurrence of apnea.

3 HEENT

- ✓ Facial puffiness → part of GBS
- ✓ Pale conjunctiva and pale buccal mucosa → anemia

4 LGS

- ✓ Thyroid enlargement → thyrotoxicosis is precipitant factor

5 RS

- ✓ **Pulmonary crackles (rales or crepitations)**

  - Result from the transudation of fluid from the intravascular space into the alveoli.
  - In patients with **pulmonary edema, rales may be heard widely over both lung fields** and may be accompanied by expiratory wheezing (cardiac asthma).
  - When present in patients without concomitant lung disease, **rales are specific for HF**.
  - Importantly, rales are frequently absent in patients with chronic HF, even when LV filling pressures are elevated, because of increased lymphatic drainage of alveolar fluid.
- ✓ **Pleural effusions**
  - Result from the elevation of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities.
  - Since the pleural veins drain into both the systemic and the pulmonary veins, **pleural effusions occur most commonly with biventricular failure.**
  - **Although pleural effusions are often bilateral in HF, when they are unilateral, they occur more frequently in the right pleural space**
- ✓ Consolidation → if there is pneumonia as precipitant (BBS).
- ✓ Friction rub → Sign of pericarditis (unlike to plural origin not associated with respiratory cycle).

6 CVS

Arterial examination

- ✓ Arterial cording from atherosclerosis → best appreciated at radial arteries
- ✓ Bruit especially over the carotid → rare but high risk for stroke
- ✓ Pistol shot over femoral artery → AR

Venous examination

- ✓ Distended neck vein (engorged and pulsatile) → suggest RSHF, TR
- ✓ Raised JVP → suggest RSHF or biventricular failure
  - JVP Normal $\leq$ 8 cm (3cm above the sternal angle) → by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5 cm.
- ✓ +ve hepatojugular reflex
  - In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated with sustained (~15s) pressure on the abdomen (positive abdominojugular reflux).
  - **Remark:** Hepatojugular reflex is important bedside test to differentiate GBS from cardiac origin vs other causes like CLD.

Precordial examination

- ✓ Hyper active precordium → suggest cardiac muscle hypertrophy (e.g. LVH)
- ✓ Silent precordium → IHD, DCMP, morbid obesity, obstructive lung disease
- ✓ Precordial bulge → rare but it can suggest long standing CHD (N.B. PDA, ASD… can reach up to adulthood)

- ✓ Cardiomegaly and ventricular hypertrophy features
    - o Displaced PMI
        - ▪ PMI usually is displaced below the 5th ICS and/or lateral to the MCL
        - ▪ Notice; in most causes of Cardiomegaly (e.g. VHD), there is displaced PMI with active precordium unlike cardiomegaly from DCMP, which result displaced PMI with silent precordium
    - o Heave (suggests hypertrophy) and thrill (suggests grade IV murmur)
        - ▪ Patients with RVH may have a sustained and prolonged left parasternal impulse (heave) extending throughout systole
        - ▪ Heave over the apex suggests LVH
    - o Sustained diffuse and thrusting PMI, Displaced AI, active precordium
        - ▪ Severe LV hypertrophy leads to a sustained PMI
- ✓ Murmur of MR and TR frequently present in patients with advanced HF
- ✓ S3 gallop in some patients and palpable at the apex
    - o An S3 (or proto diastolic gallop) is most commonly present in patients with volume overload who have tachycardia and tachypnea, and it often signifies severe hemodynamic compromise
- ✓ S4 is not a specific indicator of HF but is usually present in patients with diastolic dysfunction

7 Abdominal examination

- ✓ **Hepatomegaly**
    - o It is an important sign in patients with HF. **which is tender, smooth and with blunted edge** from cardiac congestion of liver
    - o **may pulsate during systole if TR is present**.
- ✓ **Ascites** → a late sign, occurs as a consequence of increased pressure in the hepatic veins and the veins draining the peritoneum.
- ✓ **Jaundice** → also a late finding in HF, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin.
    - o **Remark: severe hemolysis also results in jaundice: severe anemia may be a cause or precipitant of HF**
- ✓ Rarely tipped splenomegaly from IE

8 GUS

9 MSS

- ✓ **Peripheral pitting edema**
    - o **It is a cardinal manifestation of HF**, but it is **nonspecific** and usually is absent in patients who have been treated adequately with diuretics.
    - o It is **usually symmetric and dependent** in HF and
    - o **occurs predominantly in the ankles and the pretibial region in ambulatory patients.**
    - o In **bedridden patients**, edema may be found in the **sacral area (presacral edema)** and the **scrotum.**

   - Long-standing edema may be associated with indurated and **pigmented skin (Stasis dermatitis)** .

10 IS

- ✓ Pallor → Anemia
- ✓ Cyanosis and cold extremities → suggest decreased CO
    - Peripheral vasoconstriction leading to cool peripheral extremities and cyanosis of the lips and nail beds is caused by excessive adrenergic activity.

      NB: Look for skin manifestation of IE

11 NS

- ✓ Hemiparesis / hemiplegia 2ry to Cardio embolic stroke

DDX

For Dyspnea (SOB)*	For GBS#
1. CHF 2ry to *(see table about "etiologies of HF" from the discussion part below)* a. RHD b. HHD c. IHD d. CMP e. Constrictive pericarditis (Pericardial disease) f. CHD g. Arrhythmia h. IE i. Severe anemia j. Thyrotoxicosis N.B VHD can result from RVHD, IE or DVHD (for old age) 2. Pulmonary TB 3. Bronchial Asthma (severe persistent Asthma) 4. Cor pulmonale a. COPD b. Lung Abscess c. Bronchiectasis d. ILD 5. Lung ca	1. CHF → symmetrical and worsens in the evening and improves early in the morning 2. Constrictive pericarditis (usually isolated ascites) 3. CKD 4. Nephrotic syndrome → affects face first 5. CLD 6. Advanced Lymphoma (NHL) 7. Disseminated TB or SLE to pericardium (result in Constrictive pericarditis), pleura, Peritoneum… 8. Varicose veins and DVT → More of peripheral edema 9. Vasodilating drugs (e.g. CCB's) 10.? Protein losing enteropathy

* In most patients who present with classic signs and symptoms of HF, the diagnosis is relatively straightforward. However, even experienced clinicians have difficulty differentiating the dyspnea that arises from cardiac and pulmonary causes. In this regard, Echo, CXR, biomarkers, pulmonary function testing, may be useful.

* When HF develops in patients with a preserved EF, it may be difficult to determine the relative contribution of HF to the dyspnea that occurs in chronic lung disease and/or obesity.

# Ankle edema may arise secondary to varicose veins, obesity, renal disease, or gravitational effects.
Remark: If all workup for causes of ankle edema are normal consider idiopathic edema.

Ass't example

NYHA class IV, stage C, CHF 2ry to CRMVHD (MR, TR, AR) precipitated by CAP

IX

1. **Routine Laboratory Testing**
    - Patients with new-onset HF and those with chronic HF and acute decompensation should have;
        - **CBC** → **anemia** of Chronic illness or NcNc (Normo cystic normo chromic) Anemia of IE, **leukocytosis** suggests infection such as pneumonia but non-specific, leukocytosis is also minor criteria of Jones
        - **Electrolytes** → Sodium, potassium and calcium: derangement may lead to arrhythmia. Should be done if diuretics are going to be started.
        - **BUN and serum creatinine** → important for diuretics Mgt, cardio renal Sxx (elevated BUN/creatinine ratio), complication of IE(AGN)
        - **Hepatic enzymes** → May be elevated: Liver congestion
        - **Urinalysis** → hematuria from IE
        - **Urine HCG** for all women of child bearing age → pregnancy may be precipitant, peripartal cardiomyopathy
        - **PICT**
    - Selected patients should have;
        - **FBS or OGTT** → for diabetes mellitus assessment
        - **Lipid profile** → for dyslipidemia assessment
        - **TSH, if TSH is abnormal T3 and T4** → done if indicated (e.g Thyroid enlargement on palpation, if there is Thyrotoxicosis smx). **Elevated T3 & T4** with decreased TSH support **Thyrotoxicosis** as precipitant or a cause of high output HF.
        - **Remark: Hypothyroidism may result in pericardial effusion.**
2. **Echo** → can show us
    - A semiquantitative assessment of **LV size and function**

- The presence or absence of **valvular and/or regional wall motion abnormalities** (indicative of a prior MI)
- The presence of **left atrial dilation and LVH**, together with **abnormalities of LV diastolic filling** provided by pulse-wave and tissue Doppler, is useful for the assessment of **HFpEF**
- Assessing **RV size and pulmonary pressures**, which are critical in the evaluation and management of **cor pulmonale** (click here → Chapter 2; Cor pulmonale and Chronic lung disorders)
- **Vegetation**
- **Valve abnormality** in general (stenotic/regurgitant,thickening/calcification)
- **Thrombus** → common in left Auricle and mostly Associated with Atrial fibrillation
- **Septal Defect** → ASD, VSD, PDA
- **Chamber size and wall hypertrophy** → e.g. large chamber size in DCMP, septal and wall Hypertrophy in HCMP
- **EF** (Ejection Fraction) = $\frac{SV}{EDV}\, x\, 100\,\% = 50 - 60\,\%$
    - EF will be low (<30 - 40%) in Heart failure with reduced ejection fraction (HFrEF) and normal (≥50%) in Heart failure with preserved ejection fraction (HFpEF)
    - The most useful index of LV function is the EF.
    - Because the EF is easy to measure by noninvasive testing and easy to conceptualize, it has gained wide acceptance among clinicians.
    - Unfortunately, the EF has a number of limitations as a true measure of contractility, since it is influenced by alterations in afterload and/or preload.
    - Nonetheless, with the exceptions indicated above, when the EF is normal (≥50%), systolic function is usually adequate, and when the EF is significantly depressed (<30 - 40%), contractility is usually depressed
- **Movement (kinesis)** of the wall
- Minimal pericardial fluid in acute rheumatic fever

3. **CXR** → can show us
    - Cardiomegaly i.e. Cardiothoracic ratio $> 50\%$
    - To assess the state of the pulmonary vasculature, and may identify noncardiac causes of the patient’s symptoms.
        - Pulmonary edema → bat wing appearance, cephalization (Diversion of Blood vessel circulation towards the Apex), Kerl B lines
        - Although patients with acute HF have evidence of pulmonary hypertension, interstitial edema, and/or pulmonary edema, the majority of patients with chronic HF do not.
    - Consolidation → consider Pneumonia as precipitant
    - Pleural effusion → obliterated costophrenic angle, meniscus sign +ve
4. **ECG** → The major importance of the ECG is
    - To assess cardiac rhythm abnormality such as AF (Atrial Fibrillation)

    - To determine the presence of LVH and/or RVH
    - To assess presence of a prior MI (presence or absence of Q-waves)
        - STEMI/NSTEMI (ST elevation or Non-ST elevation MI)
    - Prolonged PR interval in RHD
    - A normal ECG virtually excludes LV systolic dysfunction.
    - To determine QRS width to ascertain whether the patient may benefit from resynchronization therapy (not available in our setup).

5. **APR** (acute phase reactants) → *ESR commonly done in our setup*
    - Elevated ESR & CRP are also suggestive of infection such as pneumonia but non-specific
    - ESR and CRP elevation are minor criteria of Jones.
6. **Cardiac Biomarkers** → *troponin and CK are available in most private setups of Ethiopia rather than government hospitals (for normal laboratory reference values click here →* Chapter 11; Reference Intervals for Laboratory Tests*)*
    - **Elevated troponin T, I; More specific.**
    - **CKmb also elevated: Important for re-infraction assessment.**
    - **BNP** used for prognosis and follow up
        - Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF
        - They also are elevated in HF patients with a preserved EF, albeit to a lesser degree
        - Moreover, the measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF and can be useful to achieve optimal dosing of medical therapy in select clinically euvolemic patients
        - However, it is important to recognize that natriuretic peptide levels;
            - increase with age and renal impairment
            - more elevated in women
            - can be elevated in right HF from any cause.
            - can be falsely low in obese patients.
7. **Blood culture** → for IE (S.viridans, S. fecalis, S. Aureus, HACEK)
8. **ASO titre and** DNAse → supportive evidence for ARF (common in children)
9. Cardiac MRI (usually not done in our setup)
    - MRI provides a comprehensive analysis of cardiac anatomy and function and is now the gold standard for assessing LV mass and volumes.
    - MRI also is emerging as a useful and accurate imaging modality for evaluating patients with HF, both in terms of assessing LV structure and for determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, and hemochromatosis).
10. Exercise Testing *(not applicable in our setup)*

  - Treadmill or bicycle exercise testing is not routinely advocated for patients with HF, but either is useful for assessing the need for cardiac transplantation in patients with advanced HF.
  - A peak oxygen uptake (VO_2) <14 mL/kg/min is associated with a relatively poor prognosis.
    - Patients with a VO_2 <14 mL/kg/min have been shown, in general, to have better survival when transplanted than when treated medically.
- Remark: For those who have indication for exercise ECG, link to advanced medical center.

Discussion

Before going to the details of discussion of HF, you have to know Framingham diagnostic criteria of HF, NYHA functional classification of HF, stages of HF, JONES criteria for Acute Rheumatic Fever(ARF) & Rheumatic heart disease (RHD) and modified Dukes criteria for Infective endocarditis (IE). ***(click the links written in blue*** *to refer under respective topics below)*

1.1 Heart Failure/HF/

- HF is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales.
- Because many patients present without signs or symptoms of volume overload, the term “heart failure” is preferred over the older term “congestive heart failure.”
- Heart Failure also defined as an abnormality of cardiac structure or function leading to failure of the cardiac output to meet the body’s metabolic requirements despite normal filling pressures.
- It represents an *end stage* of a number of different diseases.
- Identification of the underlying cause of the Heart Failure is central to diagnosis. It could result from VHD, IHD, HTN, CMP, thyrotoxicosis, CHD, etc.

Epidemiology

- The overall prevalence of HF in the adult population in developed countries is 2%.
- HF prevalence follows an exponential pattern, rising with age, and affects 6 - 10% of people aged >65.

- Although the relative incidence of HF is lower in women than in men, women constitute at least one-half the cases of HF because of their longer life expectancy.
- The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders, such as MI, VHD, and arrhythmias, are allowing patients to survive longer.
- The prevalence of HF in emerging nations is uncertain because of the lack of population-based studies in those countries.

Forms of CHF

- HF was once thought to arise primarily in the setting of a depressed left ventricular (LV) ejection fraction (EF); however, epidemiologic studies have shown that **approximately one-half of patients who develop HF have a normal or preserved EF** (EF $\geq 50\%$).
- Accordingly, **the historical terms "systolic" and "diastolic" HF have been abandoned,** and HF patients are **now broadly categorized into HF with a reduced EF (HFrEF**; EF $< 30 - 40\%$, formerly systolic failure) or **HF with a preserved EF (HFpEF**; EF $\geq 50\%$, formerly diastolic failure).
- Patients with a LV EF between 40 and 50% have been considered as having a **borderline or mid-range** EF.

1. HFrEF vs HFpEF ➢ See the notes above and table below (etiologies of heart failure)	
2. Right sided versus left sided:	
✓ *left sided failure:* dyspnea, orthopnea, PND	✓ *right sided failure:* peripheral edema, hepatomegaly, ascites
NB. ➢ Right sided failure usually results from left sided failure. ➢ isolated right sided failure which results from pulmonary hypertension is called *cor pulmonale*	
3. High output vs low output failure:	
high output: thyrotoxicosis, anemia, AR	**low output**: IHD, DCMP, RCMP
4. Acute vs chronic failure	
acute: ❖ extensive MI, rupture of valves, myocarditis, massive PE	chronic: ❖ DCMP, VHD

❖ predominantly systolic abnormality ❖ **pulmonary edema** or hypotension (**cardiogenic shock**) without peripheral edema	❖ BP is usually maintained, edema is common

Difference between heart failure (HF) and congestive heart failure (CHF)

HF	CHF
✓ dyspnea, orthopnea, PND, weakness and decreased exercise tolerance ✓HF symptoms without sign and smx of congestion ☛ NO Sign of congested heart failure ✓There is Murmur of Valvular lesions	✓ dyspnea, orthopnea and PND together with peripheral edema, hepatomegaly, ascites ✓ HF symptoms together with sign and smx of congestion ☛ +ve Signs of congested heart failure → refer CVS examination of Nitsbin (click here → 1.2 Cardiovascular System) ✓ There is Murmur of Valvular lesions

Etiology of heart failure (see table below)

- Any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF.
- Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions.
- **Rheumatic heart disease remains a major cause of HF in Africa** (including our country Ethiopia) and Asia, especially in the young
- **Hypertension** is an important cause of HF in the African **and African-American populations.**
- **In industrialized countries**, **coronary artery disease** (**CAD**) has become the predominant cause in men and women and is responsible for **60 - 75%** of cases of HF.
- **Hypertension** contributes to the development of HF in **75%** of patients, including most patients with CAD.
- Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.
- In **20 - 30%** of the cases of HF with a depressed EF, **the exact etiologic basis is not known** These patients are referred to as having nonischemic, dilated, or **idiopathic** cardiomyopathy.

Table; Etiologies of Heart Failure

Depressed or reduced Ejection Fraction (<40%)/HFrEF/	Preserved Ejection Fraction (>40 - 50%) /HFpEF/

➢ Coronary artery disease o **Myocardial infarction** [a] o **Myocardial ischemia** [a] ➢ Chronic pressure overload o **Hypertension** [a] o **Obstructive valvular disease (e.g. MS, AS)** [a] ➢ Chronic volume overload o **Regurgitant valvular disease** (e.g. MR. TR) o Intracardiac (left-to-right) shunting o Extracardiac shunting ➢ Chronic lung disease o **Cor pulmonale** o Pulmonary vascular disorders (e.g. Pulmonary arterial HTN) ➢ Nonischemic **dilated cardiomyopathy** o Familial/genetic disorders o Infiltrative disorders [a] ➢ Disorders of rate and rhythm o **Chronic bradyarrhythmia's** o **Chronic tachyarrhythmias** ➢ **Toxic/drug-induced** damage o Metabolic disorder [a] o Viral ➢ Chagas' disease (only in America)	➢ Pathologic hypertrophy o Primary (**hypertrophic cardiomyopathies)** o Secondary (**hypertension**) ➢ **Restrictive cardiomyopathy** o Infiltrative disorders (amyloidosis, sarcoidosis) o Storage diseases (hemochromatosis) ➢ Aging ➢ Endomyocardial disorders ➢ Fibrosis **High-Output States** ➢ Metabolic disorders o **Thyrotoxicosis** ➢ Excessive blood flow requirements o Systemic arteriovenous shunting o **Chronic anemia** ➢ Nutritional disorders **(beriberi)** o Selenium or thiamine deficiency
[a] Indicates conditions that can also lead to heart failure with a preserved ejection fraction.	

Diagnosis of HF (see IX from the approach section above)

- The diagnosis of HF is relatively straightforward when the patient presents with classic signs and symptoms of HF; however, the signs and symptoms of HF are neither specific nor sensitive.
- Accordingly, the key to making the diagnosis is to have a high index of suspicion, particularly for high-risk patients.
- When these patients present with signs or symptoms of HF, additional laboratory testing should be performed.
- SO, **Diagnosis of heart failure is clinical. But investigations are necessary to identify the underlying cause, precipitating factor, and to guide and monitor management.**

To identify the underlying cause: Echocardiography, ECG, CXR
To identify precipitating factors based on clinical evaluation (in addition to the above investigations): CBC, ESR, U/A, blood culture, TFTs, Urine HCG, Cr, BUN, etc..
To guide and monitor management: K+, Na+, Cr, BUN, ALT, AST, serum albumin.

Modified Framingham's criteria for diagnosis of CHF

- Diagnosis requires *2 major* or *1 major and 2 minor* criteria not attributed to other medical conditions

Major criteria	Minor criteria
1. PND 2. Orthopnea 3. Elevated JVP 4. S_3 gallop 5. Pulmonary rales, Pulmonary edema on CXR 6. Cardiomegaly on CXR 7. Weight loss ≥ 4.5 kg in five days in response to treatment of presumed CHF	1) Bilateral leg edema 2) Nocturnal cough 3) Dyspnea on ordinary exertion 4) Hepatomegaly 5) Pleural effusion 6) Tachycardia (HR ≥ 120 bpm) 7) Weight loss ≥ 4.5 kg 4.5 kg in five days

NYHA (New York Heart Association) Classification of Severity /Functional Capacity

Class I	Patients with cardiac disease but **without** resulting **limitation of physical activity. Ordinary physical activity does not** cause undue **fatigue, palpitations, dyspnea, or anginal pain.**
Class II	Patients with cardiac disease resulting in **slight limitation** of physical activity. They are **comfortable at rest. Ordinary physical activity** results in **fatigue, palpitation, dyspnea, or anginal pain.**
Class III	Patients with cardiac disease resulting in **marked limitation** of physical activity. They are comfortable at rest. **Less than ordinary activity** causes fatigue, palpitation, dyspnea, or angina.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. **Symptoms** of heart failure or the anginal syndrome may be **present even at rest.** If any physical activity is undertaken, discomfort is increased.

Stages of Heart Failure (WHO/AHA)

Stage A	High risk for HF (like pt with DM, HTN, Dyslipidemia…), **without structural heart disease or symptoms**
Stage B	**Structural Heart disease** with **asymptomatic left ventricular dysfunction**
Stage C	**Structural heart disease with Prior or current symptoms of HF**
Stage D	Advanced heart disease and severely symptomatic or **refractory HF**

	requiring intervention (Valvular surgery, cardiac transplant)

Pathogenesis of heart failure

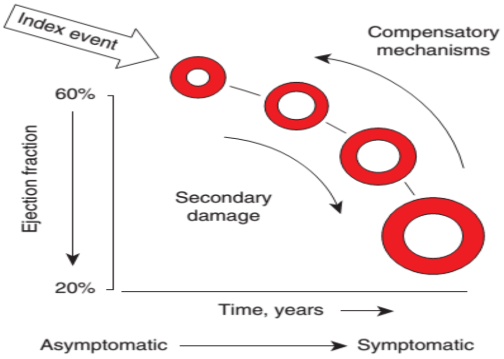

Index event
Compensatory mechanisms
60%
Ejection fraction
Secondary damage
20%
Time, years
Asymptomatic
Symptomatic

FIGURE 252-1 *(Harrison 20th edition)* **Pathogenesis of heart failure with a depressed ejection fraction.** Heart failure begins after an index event produces an initial decline in the heart's pumping capacity. After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, **sustained activation of these systems leads to secondary end-organ damage within the ventricle, with worsening left ventricular remodeling and subsequent cardiac decompensation.**

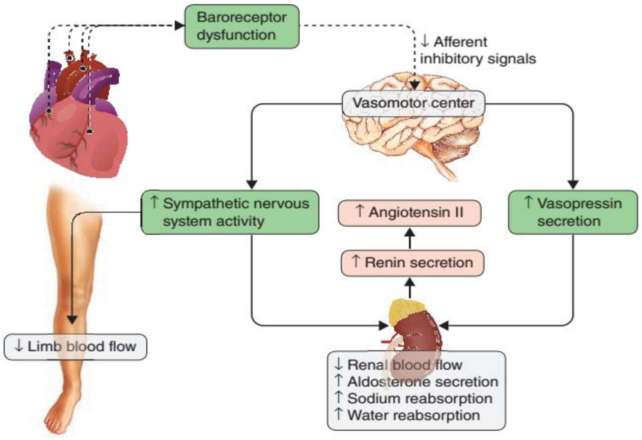

Baroreceptor dysfunction
↓ Afferent inhibitory signals
Vasomotor center
↑ Sympathetic nervous system activity
↑ Angiotensin II
↑ Vasopressin secretion
↑ Renin secretion
↓ Limb blood flow
↓ Renal blood flow
↑ Aldosterone secretion
↑ Sodium reabsorption
↑ Water reabsorption

FIGURE 252-2 **Activation of neurohormonal systems in heart failure.** The decreased cardiac output in heart failure (HF) patients results in an "unloading" of high-pressure baroreceptors (*circles*) in the left ventricle, carotid sinus, and aortic arch. This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and non-osmotic release of arginine vasopressin (AVP) from the pituitary. AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water. These afferent signals

to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles. Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short term adaptation by maintaining blood pressure, these same **neurohormonal mechanisms result in end-organ changes in the heart and the circulation, as well as to the excessive salt and water retention in advanced HF**.

Clinical manifestations of heart failure; see the approach part

1.1.1 Management of heart failure

- Management should be instituted **early** in parallel with the diagnostic work up.
- Distinctive phenotypes of presentation with diverse management targets exemplify the extensive syndrome of heart failure. These include;
    - Chronic heart failure with reduced ejection fraction **(HFrEF)**
    - Heart failure with preserved ejection fraction **(HFpEF),**
    - Acute decompensated heart failure **(ADHF),** and
    - **Advanced heart failure.**
- **Chronic heart failure with reduced ejection fraction (HFrEF)**
    - Early management evolved from symptom control to disease-modifying therapy in **HFrEF** with the advent of;
        - RAAS directed therapy
        - Beta receptor antagonists
        - Mineralocorticoid receptor antagonists
        - Cardiac resynchronization therapy and
        - Implantable cardio-defibrillators.
    - The treatment of symptomatic heart failure that evolved from a reno centric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) ushered in the era of disease-modifying therapy with neurohormonal antagonism.
    - In this regard, RAAS blockers and beta blockers form the cornerstone of pharmacotherapy and lead to attenuation of decline and improvement in cardiac structure and function with consequent reduction in symptoms, improvement in Quality of life, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths
- However, similar advances have been elusive in the syndromes of HFpEF and ADHF, which have remained devoid of convincing therapeutic advances to alter their natural history.
- **Heart failure with preserved ejection fraction (HFpEF)**
    - Therapeutic targets in HFpEF include;
        - Control of congestion

        - Stabilization of heart rate and blood pressure and
        - Efforts at improving exercise tolerance.
    - Lowering blood pressure alleviates symptoms more effectively than targeted therapy with specific agents.
    - Addressing surrogate targets, such as regression of ventricular hypertrophy in HHD, and use of lusitropic agents, such as CCB and beta receptor antagonists, have been disappointing.
- Acute decompensated heart failure (ADHF)
    - ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance.
    - The first principle of management of these patients is to identify and tackle known precipitants of decompensation.
        - Identification and management of medication nonadherence and use of prescribed medicines such as NSAIDs
        - cold and flu preparations with cardiac stimulants
        - Active infection and overt or covert pulmonary thromboembolism should be sought, identified, and treated.
        - When possible, arrhythmias should be corrected by controlling heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting ongoing ischemia with coronary revascularization or by correcting offenders such as ongoing bleeding in demand-related ischemia.
    - A parallel step in management involves stabilization of hemodynamics in those with instability.
    - **Cardiogenic pulmonary edema is most often a result of acute decompensated heart failure (ADHF)**
    - If patient has pulmonary edema or cardiogenic shock, *see the respective sections for initial management approach (click here* → Cardiogenic shock and Pulmonary edema*)*
- In advanced heart failure
    - A stage of disease typically encountered in HFrEF, the patient remains markedly symptomatic with demonstrated refractoriness or inability to tolerate full-dose neurohormonal antagonism, often requires escalating doses of diuretics, and exhibits persistent hyponatremia and renal insufficiency with frequent episodes of heart failure decompensation requiring recurrent hospitalizations. Such individuals are at the highest risk of sudden or progressive pump failure related deaths.
    - In contrast, early-stage asymptomatic left ventricular dysfunction is amenable to preventive care, and its natural history is modifiable by neurohormonal antagonism.

Principle of HF management

1. General measures
2. Treating congestion (Diuretics)
3. Correcting the precipitant factor

4. Treatment of underlying cause
5. Increase myocardial contractility
6. Prevent disease progression (Cardiac remodeling)
7. Follow up

1. General measures

- Bed rest
- Elevate bed to Semi-upright position
- Salt restriction (< 2gm or decrease added salt)
- Fluid restriction (< 1.5 - 2 L/day) for hyponatremic patients
- Administer O_2 if $SaO_2 < 90\%$.
- Activity and life style modifications:
    - ✓ Small and frequent meals
    - ✓ Restrictions on activities within the context of the specific diagnosis & the patient’s ability.
        - ➢ Competitive & strenuous sports activities are usually contraindicated
        - ➢ reduce anxiety and emotional stress
    - ✓ Weight loss for obese patients
    - ✓ Cessation of smoking
    - ✓ Avoid other CVD risk factors

2. Treating congestion (Diuretics)

- ✓ Send sample for Cr, BUN, K+ and Na+ initially and proceed with diuresis.
- ✓ For diuretic naive patients start **furosemide 20 - 40 mg IV** (if BP>90/60 mmHg) and **double the dose every 2 - 4 hour** until the urine output is >1 ml/kg/hr (40-70ml/hr) [max. 400-600mg/day or 200mg per dose].
    - ➢ Response to IV dose occurs 2-4 hours later.
    - ➢ For those already on oral furosemide, start with equal dose of IV furosemide.
    - ➢ Maintain the dose of furosemide which gave adequate response on a TID basis.
- ✓ Start **spironolactone 25 - 50 mg/day** unless $K^+ > 5.0$ meq/l or Cr > 1.6 mg/dl or GFR<30 ml/min (*main reason of adding spironolactone is to prevent hypokalemia due to furosemide*).
    - ➢ Initial dose is 25 mg po per day increased up to 100 mg BID
    - ➢ Since hyperkalemia is a life-threatening side effect of spironolactone it is contraindicated in patients with renal failure ($k^+ >5$ mmol/l or >2.5 mg/dl of CRr)
    - ➢ **Remark:** In advanced HF spironolactone dose ≥ 50mg have been found to be necessary to produce natriuresis. Studies shows with the

dose of (50-200mg) there was no significant increase in mean serum Cr or K+. However close monitoring is warranted.

- *S*pironolactone is aldosterone antagonist (mineralocorticoid receptor antagonist), ***potassium sparing diuretics***

Goal of diuresis

- *Negative fluid balance*
- *Weight loss (0.5-1kg/day)*
- *Clearance of crepitations in the lungs*
- *Decrement in edema, hepatomegaly, JVP*
- *Improvement of dyspnea, orthopnea*
- *Improvement in renal function (Cr, BUN)*

Signs of excess diuresis

- *Signs of dehydration*
- *Hypotension(overt/orthostatic)*
- *Elevated RFTs despite improvement of congestion*
- *Severe hypokalemia*

Patient not responding

- ✓ Make sure that
  - ○ Patient is taking medications as prescribed and is on salt free diet.
  - ○ Precipitating factors is managed.
  - ○ Patient is not taking drugs like NSAIDS, CCBs, BBs.

NB: *Patients with deranged renal function and hypoalbuminemia require higher doses of diuretics from the outset.*

- ✓ **Adjust the diuresis*.***
  - ○ **Increase the dose of furosemide** (max. 400 - 600mg/day) and increase **spironolactone** to 50-100mg/day.
  - ○ **Increase the frequency** of administration of furosemide 4-6 x per day. Repeated IV bolus doses are recommended that continuous infusion.
  - ○ **Remark:** there is no difference between continuous infusion and frequent bolus of furosemide for all-cause mortality, length of hospital stay and electrolyte disturbance, but continuous infusion is superior with regard to diuretic effect and reduction in BNP.
  - ○ For those patients with borderline BP continuous infusion may be preferred to avoid BP fluctuation with every bolus does of furosemide.
  - ○ **In ICU; furosemide Continuous IV infusion** by perfuser: Initial: IV bolus dose 40 to 100 mg over 1 to 2 minutes, followed by continuous IV infusion rate of 10 to 40 mg/hour; repeat loading dose before increasing infusion rate
  - ○ **Remark: in the absence of perfuser, we can add 200mg of Lasix in 1000ml NS then we can give in a drip with calculated rate.**

- If **patient not responding** with the above approaches, add ***thiazides***: hydrochlorothiazide, chlorothiazide
    - **hydrochlorothiazide** Initial: 25 mg, PO, daily or BID in the morning 30 minutes before frusemide administration; maximum daily dose: 200 mg
    - Thiazides are weaker diuretic agents useful in mild CHF alone or used in combination with loop diuretics in CHF which doesn't respond to high dose lasix

- For patients with hypertension and severe Acute MR intravenous nitroglycerin infusion can be considered in addition to diuretics. *(click and see* 1.10.2 Pulmonary edema *section)*
    - **IV nitroglycerin for Acute decompensated heart failure :**Initial: 10 to 20 mcg/minute, with subsequent titration (e.g. 10 to 20 mcg/minute every 5 to 15 minutes) up to 200 mcg/minute **or** 0.3 to 0.5 mcg/**kg**/minute with titration (if SBP ≥90 mm Hg) in increments of 20 mcg/minute every 1 to 3 minutes up to 400 mcg/minute. Patients who do not respond hemodynamically with doses of ~200 mcg/minute should be considered non-responders.

- **Remark**: Always asses for salt restriction.

Patient improving

- Decrease the dose of diuretics every day depending on patient condition.
    - goal is to use the lowest possible dose and frequency to keep patient dry.
- Change IV furosemide to PO and observe the patient with ambulation for a day or two.
- **Remark:** since PO absorption rate of Lasix is poor, use conversion rate IV to PO Lasix at 1:2 (20mg IV = 40mg PO).
    - Patients requiring higher dose of furosemide may require a double dose.

3. Correcting the precipitant factor

- ✓ Manage the identified precipitating factors.

4. Treatment of underlying cause

- Institute further management for the underlying heart disease *(see specific topic and comorbidities below)*

5. Increase myocardial contractility

- **Digoxin,** for class C or D HF and with reduced EF, 0.125 - 0.25 mg, PO, daily for positive inotropy and rate control in patients with atrial fibrillation.
    - *Effects*: - positive inotropic effect (increase myocardial contractility),

increased automaticity (arrythmia), delays AV node conduction

- ***Uses:*** - in systolic heart failure not responding to diuretic therapy, particularly when atrial fibrillation co exists with CHF
- ***Toxicity of digoxin:***
    - *Early non cardiac:* anorexia, nausea, vomiting
    - *Chronic toxicity:* weight loss, neuralgia, worsening of CHF, intractable vomiting
- ***treatment of toxicity:***
    - Discontinue digoxin
    - Treat the arrhythmia
    - Supplement potassium if hypokalemic
    - Anti-digoxin antibodies

6. Prevent disease progression (Cardiac remodeling)

- ACEI, ARBs, Beta-blockers and Aldosterone antagonists have survival benefits and anti-remodeling
    - **Remark:** Compared to ARBs, ACEI were deemed more effective in decreasing the incidence of MI and all-cause mortality in patient with HFrEF.
- If patients were already talking ACEIs and BBs (Beta blockers), they can continue to take them during hospitalization as long as they are not severely congested, are hemodynamically stable and have normal renal function.
- Temporary discontinuation or dose reduction of BB may be necessary if BP is low or borderline and patient is severely congested (pulmonary edema).
    - **Remark**: Sudden discontinuation of BBs is deleterious, if patient admitted for acute decompensated chronic HF while on BBs in the absence of contraindication (for CLASS II CHF reduce the dose of BBs by 25%, for CLASS III by 50% and for CLASS IV CHF by 75%).
- Temporary discontinuation or dose reduction of ACEIs/ARBs may be necessary if BP is low or borderline and recent renal function derangement.
- For patients in whom previous BB and ACEIs/ARBs have been discontinued consider reinitiating the drugs as soon as possible sequentially (ACEIs/ARBs followed by B blockers)
- **Note:** Initiate Beta blockers, only in stable patients or hospitalized patients after volume status has been optimized and IV diuretics, vasodilators, and inotropic agents have all been successfully discontinued. Caution should be used when initiating in patients who required inotropes during their hospital course. Increase dose gradually and monitor for congestive signs and symptoms of HF making every effort to achieve target dose shown to be effective

- **Remark:** congestion symptoms may worsen within 1-2 weeks of BBs initiation (surge of counter regulatory hormones / stress hormones).
- For HFrEF previously not taking ACEIs/ARBs or BB.
  - Start one of the ACEIs/ARBs as soon as BP and RFTs permit and escalate until discharge
  - Start one of the BB following ACEIs/ARBs when BP and PR permit and escalate until discharge
  - Start Spironolactone 25mg/d. (low EF despite maximum dose of the above two drugs)

Dose of drugs having cardiac anti remodeling effect

- ACEI
  - **Enalapril** 2.5 mg, PO, BID, titrated as tolerated to target dose of 10 mg, PO, BID (maximum: 20 mg/day).

  Alternative;
  - Lisinopril 2.5 to 5 mg, PO, daily; increase by no more than 10 mg increments at intervals no less than 2 weeks to the highest tolerated dose (maximum: 40 mg/day)
- ARBs
  - **Candesartan** 4 mg, PO, daily or alternatively 4 to 8 mg, PO, daily; double the dose at 2-week intervals, as tolerated; target dose: 32 mg once daily

  Alternative;
  - Valsartan 40 mg, PO BID; titrate dose to 80 mg, and then to 160 mg BID, as tolerated; maximum dose: 320 mg/day.
- Beta- blockers
  - **Metoprolol**; Metoprolol tartrate is short acting form, which is preferred as initial management (especially in pt's with ACS). Metoprolol succinate is long acting form
    - **Remark**: **Metoprolol succinate is superior treatment option compared to** Metoprolol tartrate in treatment of HTN, CHF and Coronary heart disease.
    - Metoprolol tartrate (Immediate release): 50 mg, PO, BID; usual dosage range: 50 to 200 mg, PO, BID; may increase dose at weekly intervals to desired effect (maximum: 400 mg/day).
    - **Metoprolol succinate** *(Extended release):* 12.5 to 25 mg once daily; may double dosage every 2 weeks as tolerated up to target dose of 200 mg/day.
  - **Carvedilol**
    - *Immediate release;* 3.125 mg, PO, BID for 2 weeks; if this dose is tolerated, may increase to 6.25 mg PO, BID. Double the dose every 2 weeks to the highest dose tolerated by patient (maximum 25mg)

        - *Extended release:* 10 mg, PO, daily for 2 weeks; if the dose is tolerated, increase dose to 20 mg, 40 mg, and 80 mg over successive intervals of at least 2 weeks. Maintain on lower dose if higher dose is not tolerated (maximum; 80 mg, daily)
    - **Bisoprolol**, 1.25 mg PO, daily; maximum dose: 10 mg, daily
- Aldosterone antagonists
    - **Spironolactone** 12.5 to 25 mg, PO, daily; maximum: 50 mg/day. If 25 mg once daily not tolerated, may reduce to 25 mg every other day
        - NB: 50mg/day patients with high dose furosemide and hypokalemia

7. Follow up during management of admitted patients

- Use the standard heart failure management follow up sheet posted by the bedside.
- V/S including orthostatic hypotension and SO_2 every 1hr until patient stabilizes and then every 4-6 hrs.
- 24 hrs urine output and fluid balance documented every 6hrs together with V/S.
- Weight every 24hrs (morning prior to eating and voiding, same scale).
    - goal is 1kg/day weight loss
- Signs of heart failure every 12hrs (JVP, basal crackles, S3 gallop, hepatomegaly, edema).
- Symptoms (dyspnea, orthopnea).
- Cr, BUN, K+, Na+ every 24hrs until patient stabilizes and then every 3-5 days and manage accordingly

Table: Sample; heart failure follow up sheet

Date	time	BP	PR	RR	T^0	Wt	SO_2	UOP	Crepitation	Hepatomegaly	JVP	Edema	Cr	Na+	K+	Sign

Before Discharge

- *Proper advice: salt consumption, activity, adherence to medications and follow up.*
- *Prescribe adequate medications and give requests for further planned outpatient investigations.*
- *Document medications with dose and further plans clearly on the discharge note.*
- *Early appointment preferably in one-week time to follow up clinic.*

Chronic OPD follow up and management

During OPD follow up

Assess

- Symptoms
- Functional status
- Adherence
- Medication tolerance
- P/E: V/S, signs of heart failure, precordial exam
- Investigations: Cr, BUN, K+, Na+ as appropriate

Manage:

- Escalate dose of ACEIs and BBs if no problem
- Consider add on therapies like spironolactone, digoxin if patient not improving after optimal diuretic, ACEI and BB therapy
- on adherence to treatment and life style modifications

Steps in the management of Heart Failure with Reduced Left Ventricular Systolic Function (HFrEF)

- Step 1: Start low dose ACEIs
- Step 2: review after two weeks: Check tolerance and side effects
    - BP, symptoms
    - Side effects ACEIs
- Step 3: Increase dose of ACEIs
    - If there is troubling cough related to the ACEIs (not because of heart failure), switch therapy to ARBs
- Step 4: review after one month and assess for Beta blocker therapy
    - If a candidate; start low dose Betablocker
- Step 5: Review after two weeks for assessment
    - If tolerated, increase dose
    - **Remark:** in stable, mildly to moderately symptomatic patients with systolic HF, initiation of therapy with BBs followed by ACEI has similarly efficacious to the opposite sequence in terms of combined mortality and all-cause hospitalization.
- Step 6: Review heart failure status (symptom, NYHA class, congestion)
    - Optimize therapy as per evidences
- Step 7: Monitor therapy at each visit (RFT, Electrolytes, optimize risk factors)
- Step 8: Early referral for refractory cases for cardiologist evaluation

Table; Treatment of chronic heart failure with reduced EF (LVEF<40%) (non-rheumatic*)

Diet, exercise	✓Avoid table salt intake, alcohol and smoking ✓Avoid stimulant caffeine other like khat, marijuana Avoid excess free water consumption ✓Exercise training in ambulating patients
ACEI ☛ Watch for azotemia, increased K+, cough, angioedema ☛ Contraindicated; pregnancy, renal artery stenosis, hyperkalemia	Escalate every 1-2 week ✓ Enalapril dose 2.5mg/day - 20mg BID *Alternative* ✓ Lisinopril dose 10-40mg/day
ARBs (ATII receptor blockers) ☛ Alternative to ACEI (cough, angioedema) but not a substitute	✓Candesartan 8-32 mg/day in 1-2 divided doses *Alternative* ✓Valsartan 40 - 80 mg PO BID
ARNI (Angiotensin-Nepro lysin Inhibitors)	Sacubitril/Valsartan combination ✓ starting with 50 mg (24mg/26mg) PO BID to increase to the most tolerable dose of 200 mg (97mg/103mg) PO BID
Beta- blockers ☛ High dose is more efficacious ☛ Caution: severe COPD/asthma, AV block(bradycardia), hypotension(shock)	Preferred: (long releasing and escalate every 2 week) ✓ Metoprolol dose 6.75 - 200mg per day ✓ Carvedilol dose 3.125-25mg BID ✓ Bisoprolol 1.25 mg Po-10 mg Po daily ✓ Nebivolol 1.25 mg PO-10 mg Po daily
Aldosterone antagonist ☛ Consider in severe HF or post MI ☛ Caution: renal function derangement, Increased K^+	✓Spironolactone 25mg po per day NB: 50mg/day patients with high dose furosemide and hypokalemia
Diuretics ☛ Patients with congestion (ie. Not only right sided but also orthopnea, PND, nocturnal cough) ☛ Watch electrolyte (Na, K, Cl) and BUN, Cr	Loop diuretics ✓Lasix(furosemide) 20mg/day up to 100- 120mg TID/QID (preferred to keep low dose) Thiazide: ✓HCT 12.5-25mg per day (congestion not improved with high dose Lasix)
Digoxin ☛ Caution: renal failure, hypokalemia, Rheumatic heart disease (MS) ☛ Use: rate control in AFFVR and added on therapy	✓Dose 0.125-0.25mg per day

Anticoagulant (OAC) ☛ **If indicated**	✓Warfarin 2.5-10mg per day
☛ *** for Chronic heart failure in rheumatic heart disease patients, click and see** Valvular heart disease (VHD) ☛ **ACEI, ARBs, Beta- blockers and Aldosterone antagonists have survival benefits and anti-remodeling effect** ☛ Choice between drugs depends on underlying heart disease ☛ Avoid combination of drugs from same group or ACEI with ARBs and spironolactone	

Prognosis

- Despite recent advances in the management of HF, the development of symptomatic HF still carries a poor prognosis.
- 30 - 40% of patients die within 1 year of diagnosis and 60 - 70% die within 5 years, mainly from worsening HF or as a sudden event (probably because of a ventricular arrhythmia).
- Although it is difficult to predict prognosis in an individual, patients with symptoms at rest (NYHA class IV) have a 30 - 70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5 - 10%. Thus, functional status is an important predictor of patient outcome

1.2 Acute Rheumatic Fever(ARF) & Rheumatic heart disease (RHD)

Acute rheumatic Fever (ARF)

- **Acute rheumatic fever (ARF) is a multisystem disease occurring as a non-suppurative complication from an autoimmune reaction to infection with group A streptococcus (GAS).**
- Although many parts of the body may be affected, almost all of the manifestations resolve completely.
- The major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared.
- **ARF and RHD are diseases of poverty.**
- **RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well.**
- Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high rates in sub-Saharan Africa, Pacific

nations, Australasia, and South and Central Asia.

- The pathogenetic pathway from exposure to group A streptococcus followed by pharyngeal infection and subsequent development of ARF, ARF recurrences, and development of RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point.
- **Crowdedness and poor hygiene lead to increased transmission of the bacteria**

Epidemiology

- **ARF is mainly a disease of children age 5 - 14 years.**
- Initial episodes become less common in older adolescents and young adults and are **rare in persons aged >30 years**.
- By contrast, **recurrent episodes of ARF remain relatively common in adolescents and young adults.**
- This pattern contrasts with the **prevalence of RHD, which peaks between 25 and 40 years**.
- There is no clear gender association for ARF, but **RHD more commonly affects females,** sometimes up to twice as frequently as males.
- The prevalence of rheumatic heart disease in the Ethiopian population among the asymptomatic school children is 19 per 1000 population.

Pathogenesis

Etiology: infection of the URT with group A, B- hemolytic streptococcus

- any strain has the potential to cause it
- repeated pharyngitis is required to prime the immune system before the development of ARF

Basic pathogenesis still unknown, but there are two theories postulated to explain RF

- 1st: **toxic effect** of extra-cellular toxins produced by strep on target organs such as myocardium, valves, synovium & brain **(cytotoxicity theory)**
- 2nd: **most popular hypothesis is immunologic damage** on target organs as a result of antigenic similarity b/n strep cellular components & human tissue **(hypothesis of molecular mimicry)**
  - ✓ Strep M-protein shares certain amino acid sequence with some human tissue, this is supposed to lead to cross reactivity b/n the organism & human host

Clinical features

- Incubation period of ~3 weeks (1 - 5 weeks)
  - The clinical features of ARF occur 2 - 3 weeks following a streptococcal throat infection
  - The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months.
- Although many patients report a prior sore throat, the preceding GAS infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing.
- **The most common clinical features are Polyarthritis (60 - 75%) and rheumatic carditis (50 - 60%).**
- The prevalence of **chorea** in ARF varies substantially between populations, ranging from **<2 to 30%.**
- **Erythema marginatum and subcutaneous nodules are now rare**, being found in <5% of cases.

Heart involvement (Rheumatic carditis)

- **Up to 60% of patients with ARF progress to RHD.**
- **ARF causes pan carditis,** affecting the pericardium (pericarditis), epicardium, myocardium (myocarditis, sometimes manifest as conduction system disease), and endocardium (valvulitis).
- **Valvular damage is the hallmark of rheumatic carditis.**
  - **The mitral valve is almost always affected**, sometimes together with the aortic valve
  - **Isolated aortic valve involvement is rare.**
  - Damage to the pulmonary or tricuspid valves is usually secondary to Increased pulmonary pressures resulting from left-sided valvular disease.
  - Early valvular damage leads to regurgitation.
  - Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop
  - Therefore**, the characteristic manifestation of carditis in previously unaffected individuals is MR, sometimes accompanied by AR.**
  - **MR is the most common early valvular manifestation and may be accompanied by AR and/or uncommonly by TR; isolated AR is less common**
  - **Heart failure (HF) and left ventricular (LV) dilation in patients with ARF are caused chiefly by severe valve disease (mainly MR with or without AR)**
- Myocardial inflammation may affect electrical conduction pathways, leading **to P-R interval prolongation** (first-degree AV block or rarely higher-level block) and **softening** of S1.
- People with **RHD are often asymptomatic for many years** before their valvular disease progresses to cause cardiac failure.

- Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it.

Joint involvement

- **The most common form of joint involvement in ARF is arthritis** (i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., **polyarthritis**)).
- **Polyarthritis is typically migratory**, moving from one joint to another over a period of hours.
- **ARF almost always affects the large joints**, most commonly the knees, ankles, hips, and elbows, **and is asymmetric**.
- The pain is severe and usually disabling until anti-inflammatory medication is commenced.
- Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria.
- Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis.
- In some populations, aseptic mono-arthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established.
- **The joint manifestations of ARF are highly responsive to salicylates and other NSAIDs.**
    - Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

Chorea

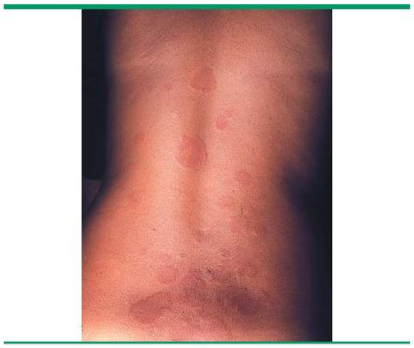
- Sydenham's chorea **commonly occurs in the absence of other manifestations**, follows a prolonged latent period after GAS infection, and is **found mainly in females**.
- The choreiform movements affect particularly the **head** (causing characteristic **darting movements of the tongue) and the upper limbs**.
- They may be generalized or restricted to one side of the body (hemi-chorea).
- In mild cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living.
- There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the choreiform movements (which usually resolve within 6 weeks but sometimes may take up to 6 months).
- **Clinical maneuvers to elicit features of chorea** include:
    - **Milkmaid's grip**
    - **spooning and pronation of the hands during extension**

- **Wormian darting movements of the tongue upon protrusion**, and
- **Examination of handwriting** to assess fine motor

Skin manifestations

- Erythema marginatum
  - **The classic rash of ARF is *erythema marginatum***, which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge.
  - The rash is evanescent, appearing and disappearing before the examiner's eyes.
  - **It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.**

Erythema marginatum



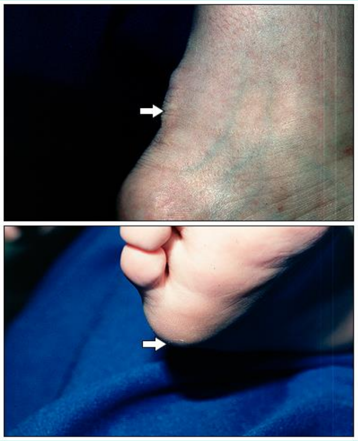
This image of the back of a patient with acute rheumatic fever shows the characteristic rash, erythema marginatum. Note the erythematous lesions with pale centers and rounded or serpiginous margins.

Erythema marginatum

A closer view of erythema marginatum in a patient with acute rheumatic fever.

- Subcutaneous nodules
  - occur as **painless, small (0.5 - 2 cm), mobile lumps beneath the skin overlying bony prominences**, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae.
  - They are a delayed manifestation, appearing 2 - 3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are **commonly associated with carditis**.

Rheumatic subcutaneous nodules



Rheumatic subcutaneous nodules are usually located near tendons or over a bony surface or prominence (see arrows). The overlying skin is not inflamed and typically can be moved over the nodules. The diameter varies from a few millimeters to 1 to 2 centimeters.

Other features

- **Fever** occurs in most cases of ARF, although rarely in cases of pure chorea.
    - Although high-grade **fever (≥39°C)** is the rule, lower grade temperature elevations are not uncommon.
- **Elevated acute-phase reactants** are also present in most cases.

Evidence of a preceding GAS infection

- With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding GAS infection is essential in making the diagnosis of ARF.
- Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed.
    - The most common serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers.

Confirming the diagnosis

- Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating GAS infection, and the exclusion of other diagnoses.
- This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the *Jones criteria*) to aid in the diagnosis.
- The most recent revision of the Jones criteria **(see Table Below)** require the clinician to determine if the patient is from a setting or population known to experience low rates of ARF.

- For this group, **there is a set of “low-risk” criteria**; for all others, there is a set of **more sensitive criteria.**

Table; Jones Criteria

For All Patient Populations with Evidence of Preceding GAS Infection	
Diagnosis: initial ARF	2 major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 major or 1 major and 2 minors or 3 minors
Low-risk populations [a]	Moderate- and high-risk populations
Major Criteria*	
Carditis [b] ➢ Clinical and/or subclinical	Carditis ➢ Clinical and/or subclinical
Arthritis ➢ Polyarthritis only	Arthritis ➢ Monoarthritis or polyarthritis ➢ Polyarthralgia [c]
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
Minor Criteria	
Polyarthralgia	Monoarthralgia
Fever ($\geq 38.5^{0}$C)	Fever ($\geq 38.5^{0}$C)
ESR ≥ 60 mm in the first hour and/ or CRP ≥ 3.0 mg/dL [d]	ESR ≥ 30 mm/h and/or CRP ≥ 3.0 mg/dL [d]
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

[a] Low-risk population are those with ARF incidence ≤ 2 per 100,000 school-age children or all-age rheumatic heart disease prevalence of ≤ 1 per 1000 population per year (Ethiopia is under ”high risk populations” category).

[b] Subclinical carditis indicates echocardiographic valvulitis.

[c] Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and Subcutaneous nodules are rarely “standalone” major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.

[d] CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

Abbreviations: ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. GAS, Group A Streptococcal

*Mneumonic for major criteria → JONES

J → Polyarthritis (Migratory Joint pain)

♥ → Pan Carditis

N → Subcutaneous Nodules

E → Erythema marginatum

S → Sydenham Chorea

Recommended Tests in Cases of Possible ARF

- Recommended for All Cases
    - CBC → leukocytosis
    - ESR and CRP → raised
    - Blood cultures if febrile
    - ECG
        - If prolonged P-R interval or other rhythm abnormality, repeat in 2 weeks, and again at 2 months if still abnormal
    - Echo
        - New or worsening regurgitant murmur, minimal pericardial fluid
        - Consider repeating after 1 month if negative
    - Chest x-ray
        - If clinical or echo evidence of carditis
    - Throat swab
        - Preferably before giving antibiotics
        - Culture for group A streptococcus
    - Antistreptococcal serology:
        - Both anti-streptolysin O and anti-DNase B titers
        - If available (repeat 10 - 14 days later if first test not confirmatory)
- Tests for Alternative Diagnoses, Depending on Clinical Features
    - Repeated blood cultures if possible endocarditis
    - Joint aspirate (microscopy and culture) for possible septic arthritis
    - Copper, ceruloplasmin, antinuclear antibody, drug screen for choreiform movements
    - Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis

Management of ARF

- There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

Non-pharmacologic

- ✓ **Bed rest** if the patient has **severe rheumatic carditis or arthritis/arthralgia only.**
    - Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.
- ✓ Salt restriction if there is associated Heart Failure.

Pharmacologic

5 approaches

1. **Antibiotic therapy**
    - ✓ All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.
    - ✓ Penicillin is the drug of choice and can be given orally
        - Penicillin V, 500 mg [250 mg for children ≤27 kg] PO, BID, for 10 days or
        - Amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days or
        - benzathine penicillin G, 1.2 million units (600,000 units for children ≤27 kg), IM, stat
    - ✓ for more, refer tonsillopharyngitis management (click here → 3.7.2 Acute tonsillopharyngitis (የቶንሲል በሽታ ፣ የአንቃር እና ጉሮሮ ብግነት))

2. **Anti-inflammatory therapy** (ASA, and NSAID's)
    - These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed.
    - They are of no proven value in the treatment of carditis or chorea.
        - Those with carditis without cardiomegaly or CHF may benefit from aspirin therapy
    - **Aspirin is the drug of choice**[1]

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[1] **Aspirin dose from UpToDate 2018. Pediatricians in Ethiopia recommend the UpToDate dose** (the dose on the text is from Harrison 20th edition)

Migratory polyarthritis, with carditis without cardiomegaly or CHF*:*

- Initial: 100 mg/kg/day, PO, QID for 3 to 5 days, followed by 75 mg/kg/day, PO, QID for 4 weeks.

    - 50 - 60 mg/kg/day, up to a maximum of 80 - 100 mg/kg per day (4 - 8 g/d in adults) in 4 - 5 divided doses.
    - When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses can have the dose reduced to 50 - 60 mg/kg/day for a further 2 - 4 weeks.
    - Fever, joint manifestations, and elevated acute phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period.
    - Add a GI prophylaxis - PPI (e.g. Omeprazole 20mg, P.O., BID)
  - Naproxen is a suitable alternative to aspirin
    - 10 - 20 mg/kg/day PO, BID

3. **Treat CHF (see the respective topic)**

- **Glucocorticoids**
  - **The use of glucocorticoids in ARF remains controversial.**
  - Many clinicians treat cases of **severe carditis** (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects.
  - Its use was Considered **in Patients with carditis and cardiomegaly or CHF**
  - **If used, prednisone or prednisolone** is recommended
    - 1 - 2 mg/kg/day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks.
    - prednisone is 2 mg/kg/day, QID, for 2-3 wk followed by a tapering of the dose that reduces the dose by 5 mg/24 hr every 2-3 days.
    - At the beginning of the tapering of the prednisone dose, aspirin should be started at 75 mg/kg/day, QID, for 6 wk.

4. **Sydenham chorea treatment if present**
   - Medications to control the abnormal movements do not alter the duration or outcome of chorea.
   - **Milder cases** can usually be managed by providing a **calm environment.**

Carditis and cardiomegaly or CHF:

- At the beginning of the tapering of the prednisone dose, aspirin should be started at 75 mg/kg/day, PO, QID for 6 weeks

- In patients with **severe chorea**
  - **carbamazepine or sodium valproate is preferred to haloperidol.**
    - A response may not be seen for 1 - 2 weeks, and medication should be continued for 1 - 2 weeks after symptoms subside.
  - **Corticosteroids** are effective and lead to more rapid symptom reduction in chorea.
    - They should be considered in **severe or refractory cases.**
    - **Prednisone or prednisolone**, 0.5 mg/kg, PO, daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen.

5. Prevention

Primary prevention:

- **Ideal**: eliminating risk factors for GAS infection which are over crowdedness and poor hygiene (the antibiotics discussed above)
- If sore throat is treated within 9 days of commencement ARF will be prevented

Secondary prevention

- **The mainstay of controlling ARF and RHD is secondary prevention.**
- Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences.
- Long term antibiotic prophylaxis is required for those patients who have sustained an episode of rheumatic fever (see the table below)

  - First line
    - A single IM injection of benzathine penicillin G (600,000 IU for children ≤ 27kg and 1.2 million IU for those >27kg and adults) every 4 weeks (i.e. monthly)
      - ☛ It can be given every 3 weeks, to persons considered to be at particularly high risk.
  - Alternative
    - penicillin V, 250 mg, PO, BID For 10 days, every month or
    - amoxicillin 500 mg po TID for 10 days, every month
  - For Penicillin-allergic patients
    - Erythromycin, 250mg, P.O. BID for 10 days, every month

Table; Duration of secondary prophylaxis	
Category of Patient	**Duration of Prophylaxis**
Rheumatic fever **without carditis**	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever **with carditis** with no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever **with persistent valvular disease**, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes **lifelong** prophylaxis

Follow UP

- Weekly or every 2 weeks follow up of ESR and CRP (normalize within 4-6 weeks)
- Echo after 1 month to see the progression of carditis

Prognosis of ARF

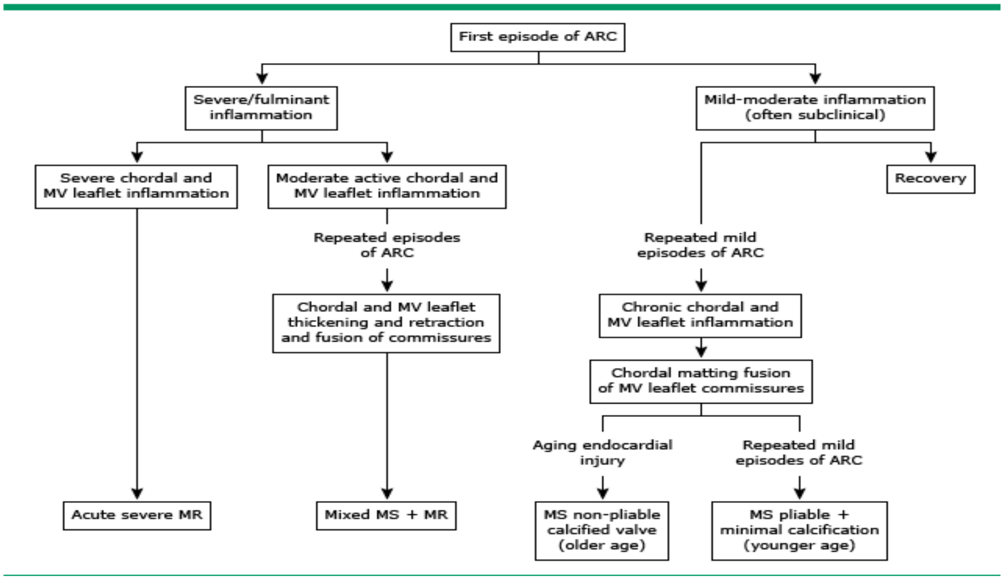
- Untreated ARF stays for 12 weeks
- 60 % of patients with ARF develop RHD
- The arthritis and chorea of acute rheumatic fever resolve completely without sequelae.
- The long-term sequelae of rheumatic fever are essentially limited to the heart.
- ≈50-70% of patients with carditis during the initial episode of acute rheumatic fever recover with no residual heart disease.
- Recurrence risk is ≈ 50% following each GAS pharyngitis after initial ARF.
- The risk of recurrence is highest in the 1st 5 yrs after the initial episode and decreases with time.
- ≈ 20% of patients who present with “pure” chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yrs

Rheumatic Heart Disease (RHD)

- RHD is a Late Sequela of ARF.
- Up to 60% of patients with ARF progress to RHD (i.e. Approximately 50 - 60 % of those with evidence of carditis develop organic valvular damage)
  - ✓ The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of one or more of the heart valves.
  - ✓ With repeated attacks of rheumatic fever, new verrucae form near the previous ones, and the mural endocardium and chordae tendineae become involved

- Up to 75% of patients with documented recurrences of RF have some form of valvular disease after 4 to 5 years of follow-up
- RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well
- RHD, peaks between 25 and 40 years.
- RHD more commonly affects females, sometimes up to twice as frequently as males.
- RHD remains a major cause of cardiovascular disease in developing nations
  - ✓ In Africa valvular disease is encountered in the young, not infrequently in children of school-going age or young females of child-bearing potential, and with a course that is much more rapid.
- RHD accounts for 12 - 65% of hospital admissions related to cardiovascular disease and 2 - 10% of hospital discharges in some developing countries.
  - ✓ **In Ethiopia, RHD Accounts for 50 % of all Cardiovascular disease admisions to hospital and common in females**

Pathogenesis of rheumatic mitral valve disease


First episode of ARC
Severe/fulminant inflammation
Mild-moderate inflammation (often subclinical)
Severe chordal and MV leaflet inflammation
Moderate active chordal and MV leaflet inflammation
Recovery
Repeated episodes of ARC
Repeated mild episodes of ARC
Chordal and MV leaflet thickening and retraction and fusion of commissures
Chronic chordal and MV leaflet inflammation
Chordal matting fusion of MV leaflet commissures
Aging endocardial injury
Repeated mild episodes of ARC
Acute severe MR
Mixed MS + MR
MS non-pliable calcified valve (older age)
MS pliable + minimal calcification (younger age)

ARC: acute rheumatic carditis; MS: mitral stenosis; MV: mitral valve; MR: mitral regurgitation.

Clinical features

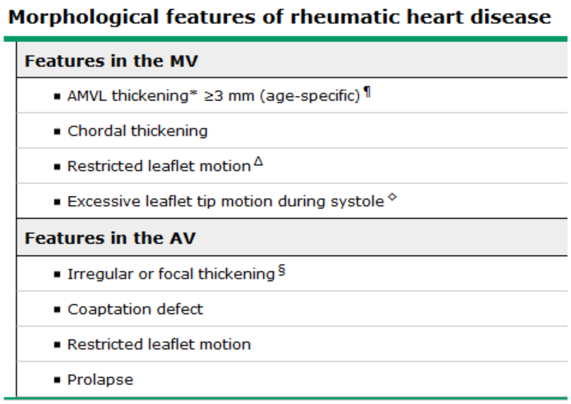
- People with **RHD are often asymptomatic for many years** before their valvular disease progresses to cause cardiac failure.
- While chronic RHD occurs only as a sequalae of ARF, the majority of patients with RHD lack a history of past ARF, suggesting that the diagnosis of ARF is frequently missed with the initial or recurrent insults being subclinical or not detected.
- RHD generally presents as valve disease, which may or may not be detected by a murmur.

- The frequency of symptoms and signs of HF (eg, dyspnea and evidence of pulmonary edema) and of embolic events (eg, stroke) among patients with RHD varies depending upon the stage of valve disease at diagnosis.
- In endemic areas presentation with advanced disease is common
- **Complications of RHD** may happen such as
  - **HF**
  - **Atrial fibrillation**
  - **IE**
  - **Pulmonary hypertension, and**
  - **Cardio-embolic stroke (less common)**
- Multivalvular disease (varying combinations of stenotic or regurgitant lesions involving the mitral and aortic valves) is the predominant abnormality in older adults
  - The Mitral Valve is involved (MR with or Without MS) in nearly all cases of RHD, including those with other affected valves.
  - The aortic valve is involved (AR with or Without AS) in approximately 20 to 30 % of cases.
  - The tricuspid valve is commonly affected, but tricuspid valve disease is frequently subclinical until surgery is required.
    - RHD can cause organic TR and/or tricuspid stenosis.
    - Rheumatic tricuspid valve disease is almost invariably associated with Mitral Valve disease
  - Pulmonic valve involvement is rare.
- **So, the Clinically detectable valvular findings from RHD patients in our setup are MR and TR with/without AR**
- The diagnosis of RHD is generally confirmed by transthoracic echocardiography, which enables assessment of valve morphology and severity of valve dysfunction (regurgitation and/or stenosis).
  - Echocardiography is also used to assess left and right ventricular size and function and may enable estimation of pulmonary artery systolic pressure.
- for more, see Rheumatic carditis above and VHD below

World Heart Federation criteria for the echocardiographic diagnosis of RHD

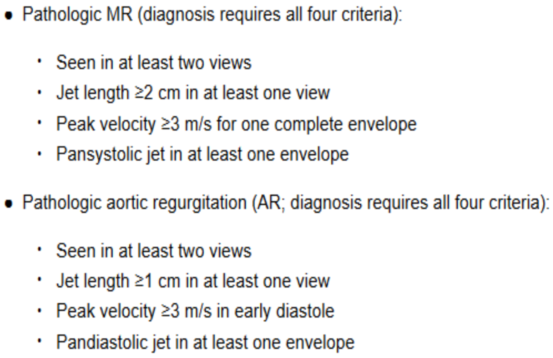
- **Definite RHD** is diagnosed if one or more of the following criteria are present: (For patients with no history of ARF)
  - Pathologic MR and at least two morphologic MV features of RHD (see table below).
  - MS mean gradient ≥4 mmHg (congenital MV anomalies and nonrheumatic mitral annular calcification must be excluded).
  - Pathologic AR and at least two morphologic features of RHD of the MV.
    - For individuals ≤20 years old, bicuspid aortic valve, dilated root, and hypertension must be excluded.

  - For individuals ≤20 years old, borderline disease of both the aortic valve and Mitral Valve.
    - Combined AR and MR, particularly in high-prevalence regions and in the absence of CHD, is regarded as rheumatic.
  - For individuals <35 years old, pathologic AR, and at least two morphologic features of RHD of the aortic valve.
    - Bicuspid aortic valve, dilated aortic root, and hypertension must be excluded.
- **Borderline RHD** only applies to individuals ≤20 years old and is present if one of the following criteria is present: (For patients with no history of ARF)
  - At least two morphologic features of RHD of the MV without pathologic MR or MS
  - Pathologic MR
  - Pathologic AR
- For patients with history of ARF
  - Consider the diagnosis of RHD definite if there is a typical valvular abnormality (as defined by one or more morphologic World Heart Federation criteria of RHD (table below) **or**
  - Evidence of World Heart Federation criteria for pathologic regurgitation).



Morphological features of rheumatic heart disease

Features in the MV
AMVL thickening* ≥3 mm (age-specific)[¶]
Chordal thickening
Restricted leaflet motion[Δ]
Excessive leaflet tip motion during systole[◇]
Features in the AV
Irregular or focal thickening[§]
Coaptation defect
Restricted leaflet motion
Prolapse



- Pathologic MR (diagnosis requires all four criteria):
  - Seen in at least two views
  - Jet length ≥2 cm in at least one view
  - Peak velocity ≥3 m/s for one complete envelope
  - Pansystolic jet in at least one envelope
- Pathologic aortic regurgitation (AR; diagnosis requires all four criteria):
  - Seen in at least two views
  - Jet length ≥1 cm in at least one view
  - Peak velocity ≥3 m/s in early diastole
  - Pandiastolic jet in at least one envelope

MV: mitral valve; AMVL: anterior mitral valve leaflet; AV: aortic valve; RHD: rheumatic heart disease. ¶: ≥3 mm for individuals aged ≤20 years; ≥4 mm for individuals aged 21 to 40 years; ≥5 mm for individuals aged >40 years

General management of RHD

- Patients with rheumatic valve disease should undergo periodic clinical and echocardiographic evaluation with frequency based upon the severity of disease, as described for individual valve lesions In VHD below.
- Standard indications for valve intervention apply with choice of procedure (eg, mitral valve repair or replacement) based upon patient characteristics and available treatment options.
- As noted above, secondary prevention of rheumatic fever is recommended in patients with history of ARF and/or RHD.
- Annual influenza vaccination and meticulous dental hygiene with annual check-ups are recommended for patients with RHD.

- Prophylaxis against IE is recommended for patients with prosthetic heart valves or a previous history of IE who undergo invasive dental procedures.
- Management of HF and other complications if present.

1.3 Valvular heart disease (VHD)

- ❖ Majority of VHD are 2ry to CRMVHD (Chronic rheumatic multivalvular heart disease) for all age groups followed by degenerative VHD in old age.
- ❖ Rheumatic fever is the dominant cause of VHD in developing and low-income countries.
- ❖ The prevalence of VHD increases significantly with age for both men and women.
    - Important left-sided valve disease may affect as many as 12 - 13% of adults aged >75 years
- ❖ Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation.

1. Aortic Regurgitation (AR)

- Also called aortic insufficiency
- This condition is due to inadequate closure of the aortic valve leaflets.
- For acute aortic regurgitation, mortality is particularly high without surgical repair.

Causes

✓Acute
- IE
- Aortic dissection
- Trauma (Iatrogenic during a failed replacement surgery)

✓Chronic
- Primary valvular disease:
    - Rheumatic fever (RHD)
    - IE
    - Congenital Bicuspid aortic valve
    - SLE
    - Syphilitic aortitis
    - Ankylosing spondylitis.
    - Myxomatous (prolapse)
- Aortic root disease: widening of the aortic annulus and separation of the aortic leaflets are responsible for the AR. causes include;
    - ✓ Aortic dissection

- ✓ Systemic severe HTN
- ✓ Cystic medial degeneration of the ascending aorta
- ✓ Marfan syndrome
- ✓ Bicuspid aortic valve
- ✓ Nonsyndromic familial aneurysm
- ✓ Aortitis
- ✓ Idiopathic dilation of the aorta
- ✓ Annuloaortic ectasia
- ✓ Osteogenesis imperfecta

Clinical Features

Symptoms

- ☛ Dyspnea on exertion, PND, orthopnea
- ☛ Palpitations–worse when lying down
- ☛ Angina
- ☛ Cyanosis and shock in acute AR (medical emergency)
- ☛ Uncomfortable awareness of the heartbeat
- ☛ Head pounding

Physical examination

- ☛ *Widened pulse pressure*–markedly increased systolic BP, with decreased diastolic BP.
- ☛ Active precordium with displaced PMI
- ☛ Murmur of AR
- ☛ Peripheral signs of AR
  - ✓ ***deMusset's sign*** — head bob occurring with each heart beat
  - ✓ ***Traube's sign*** — a pistol shot pulse (systolic and diastolic sounds) heard over the femoral arteries
  - ✓ ***Duroziez's sign*** — a systolic and diastolic bruit heard when the femoral artery is partially compressed
  - ✓ ***Quincke's pulses*** — capillary pulsations in the fingertips or lips
  - ✓ ***Mueller's sign*** — systolic pulsations of the uvula
  - ✓ ***Becker's sign*** — visible pulsations of the retinal arteries & pupils
  - ✓ ***Hill's sign*** — popliteal cuff systolic pressure exceeding brachial pressure by more than 60 mmHg
  - ✓ ***Mayne's sign*** — more than a 15 mmHg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position
  - ✓ ***Rosenbach's sign*** — systolic pulsations of the liver
  - ✓ ***Gerhard's sign*** — systolic pulsations of the spleen

Diagnosis

- CXR findings: Enlarged cardiac silhouette, dilated aorta
- ECG findings: LVH
- Echocardiogram
  - Assess LV size and function
  - Look for dilated aortic root and reversal of blood flow in aorta
  - In acute AR, look for early closure of mitral valve

Serial monitoring

- **Mild** chronic AR- **clinical evaluation yearly** and routine **echo every 2-3 years**
- **Moderate AR - echo every 1-2 years**
- **Severe AR - echo yearly**

Treatment

- Start **enalapril 2.5mg po/day and escalate or amlodipine 5-10mg po/day** for the following patients
  - Symptomatic severe AR with LV dilation
  - Asymptomatic severe AR with LVEF <50%
- Patients with congestion- refer to pulmonary edema and cardiogenic shock management
- Severe AR with reduced LVEF- refer to the management of HFrEF
  - **N.B.** avoid the use of beta blockers in patients with severe AR
- Endocarditis prophylaxis- not indicated
- Pregnancy — should be avoided in the following patients
  - NYHA class III to IV symptoms
  - LVEF <40%
  - Marfan syndrome
- **Indications for surgical interventions-** patients who can afford and have the following indications should undergo **aortic valve replacement or repair**
  - Symptomatic severe chronic AR
  - Asymptomatic severe chronic AR and LVEF <50%
  - Severe chronic AR and severe LV dilatation- LVEDD >75mm or LVESD >55mm
  - Severe AR with coronary artery disease requiring bypass graft surgery

2. TR (Tricuspid Regurgitation)

Causes

- Primary (organic)
  - Rheumatic fever/RHD

  - IE
  - Papillary muscle injury (post-MI)
  - Myxomatous (tricuspid valve prolapse)
  - Leaflet trauma
  - Radiation
  - Carcinoid heart disease
  - Endomyocardial fibrosis
  - Congenital Heart disease in children (Ebstein’s malformation of the tricuspid valve)
- Secondary (functional)
  - More than 80% of TR cases encountered in clinical practice are secondary (functional)
  - RV and tricuspid annular dilatation due to multiple causes of RV enlargement such as
    - MI (i.e. remodeling post-RV **MI)**
    - Cardiomyopathy
    - Atrial fibrillation (AF)
    - Longstanding pulmonary HTN
    - Left-sided valve disease

Clinical Features

Symptoms

- Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances.
- Fatigue and exertional dyspnea are early symptoms of isolated, severe TR.
- As the disease progresses
  - Cervical pulsations
  - Abdominal fullness/bloating
  - Loss of appetite
  - Weight loss
  - Painful swelling of the lower extremities.

Signs

- Distended neck veins (common finding)
- Marked hepatomegaly with systolic pulsations
- Ascites
- Pleural effusions
- Leg edema
- Positive hepatojugular reflux sign.
- Left parasternal heave
- Murmur of TR
  - A blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo’s sign) and reduced during expiration or the strain phase of the Valsalva maneuver
- AF is usually present in the chronic phase of the disease.

Diagnosis

- ECG
  - inferior Q-wave MI suggestive of a prior RV MI
  - RVH
  - RA enlargement
  - AF
  - a bizarre right bundle branch block-type pattern with preexcitation in patients with Ebstein's anomaly
- CXR
  - RA and RV enlargement, depending on the chronicity and severity of TR
- TTE (Trans thoracic echo) is usually definitive with demonstration of
  - Diagnosis and assessment of TR
  - RA dilation and RV volume overload
  - Prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets with annular dilatation
  - In patients with severe TR, the CO is usually markedly reduced

Treatment

- **Diuretics** can be useful for patients with severe TR and signs of right heart failure. Loop diuretics like furosemide are typically used
- **An aldosterone antagonist** may be particularly helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion.
- **If heart failure due to left ventricular systolic dysfunction** is present, standard therapy, including **beta-blockers and ARB's** are recommended
- Correction of pulmonary hypertension can result in improvement in functional TR, so causes of pulmonary hypertension (such as HF, MS, and chronic thromboembolic pulmonary disease) should be addressed
- **Indications for surgical intervention (**Tricuspid valve surgery**)**
  - For patients with severe TR who are undergoing left-sided valve surgery
  - For treatment of moderate TR in patients undergoing left-sided valve surgery who have
    - Tricuspid annular dilation (>40 mm)
    - A history of right heart failure, or
    - Pulmonary arterial hypertension.
  - For treatment of severe, primary TR with right heart failure not responsive to standard medical therapy
  - Progressively declining RV systolic function.

3. MR (Mitral Regurgitation)

- This condition is due to inadequate closure of the mitral valve.
- It could be acute or chronic.
- Acute form is associated with much higher mortality

Causes

- Acute
  - IE (most often *S. aureus*)
  - Papillary muscle rupture (Post MI) or dysfunction (from ischemia)
  - Chordae tendineae rupture
  - Blunt trauma
- Chronic
  - **Primary MR** - is due to primary abnormality of the valve apparatus. Common etiologies include
    - Rheumatic fever/RHD
    - IE
    - Mitral valve prolapse (MVP)
    - Trauma
    - Congenital (cleft, AV canal)
  - **Secondary (functional) MR**- is due to LV dilatation resulting in annular dilatation of the mitral valve. Common causes include
    - IHD
    - DCMP
    - HCMP
    - Chronic Atrial Fibrillation with Left Atrial enlargement and annular dilatation
  - Mitral annular calcification
    - may include elements of both primary and secondary MR as the disease process may encroach on the leaflets, impair the normal sphincteric function of the annulus, or both

Clinical Features

Symptoms

- ✓ Dyspnea on exertion, PND, orthopnea
- ✓ Palpitations
- ✓ Later LV failure like Pulmonary edema

Signs

- ✓ Active precordium with displaced PMI
- ✓ Apical systolic thrill
- ✓ S3 gallop
- ✓ Murmur of MR

Diagnosis

- ✓ CXR findings: Cardiomegaly, dilated LV, pulmonary edema.
- ✓ ECG: AFib
- ✓ Echocardiogram: MR; dilated LA and LV; decreased LV function.
  - ☛ (Doppler and color flow studies) to diagnose the etiology & assess the severity of MR

Serial monitoring- follow-up echocardiography should be done based on the severity of MR

- **Mild MR with no** evidence of LV enlargement, LV dysfunction, or pul. HTN- **yearly clinical monitoring** is enough. Repeat echocardiography at these visits is not necessary in the absence of clinical evidence of worsening MR
- **Moderate MR- echo** should be done **yearly**, or sooner if symptoms occur
- **Severe MR**- **echo** should be done **every 6-12 months**, or sooner if symptoms occur.

Treatment

- Depends on the presence or absence of symptoms.
  - **Asymptomatic patients-** need only close follow-up.
    - If patients have associated **hypertension**, it should be treated with **enalapril or amlodipine**
  - **Symptomatic patients-** need medical therapy
    - **Lasix 40mg po BID and escalate** till the congestion is relieved
    - Start **enalapril 2.5mg po/day and escalate** up to 20mg po/day or maximally tolerated dose
    - If LVEF < 40%- refer to the protocol for heart failure with reduced ejection fraction
  - Atrial fibrillation- refer to AF management protocol
  - Anticoagulation- similar to patients with mitral stenosis
  - Endocarditis prophylaxis- not indicated unless prior IE
  - Prevention of rheumatic recurrence- similar to patients with rheumatic MR
  - **Indications for surgical intervention-** patients who can afford and have the following indications should be referred early to undergo **mitral valve repair or replacement**
    - Symptomatic severe MR
    - Asymptomatic severe MR with one of the following factors
      - LVEF<60% or LVESD >40mm
      - New onset AF
      - Pulmonary hypertension

4. Mitral Stenosis (MS)

- The disease is more common in women.
- Patients are usually asymptomatic until the mitral valve area is reduced to approximately 1.5 cm^2 (normal valve area is 4 - 6 cm^2).
- **Severity**- depends on mitral valve area (MVA)
  - Mild MS → MVA 1.5-2 cm^2
  - Moderate MS → MVA 1.0-1.5 cm^2
  - Severe MS → MVA<1 cm^2

Etiology

- Rheumatic fever/RHD is the leading cause of MS (>95%)

- Other less common etiologies include
  - IE with large vegetations
  - Congenital (parachute valve, cor triatriatum)
  - Severe mitral annular calcification with leaflet involvement
  - SLE
  - RA
  - Myxoma

Clinical Features

Symptoms

- Exertional dyspnea, orthopnea, PND
- Palpitations
- Hemoptysis
- Thromboembolism: often associated with AF
- If RV failure occurs, ascites and edema may develop

Signs

- Murmur of MS.
- Irregularly irregular pulse
- With long-standing disease, will find signs of RVF (e.g., right ventricular heave, raised JVP, hepatomegaly, ascites) and/or pulmonary HTN (loud P_2).
- Basal rales on the chest, acute pulmonary edema.
- All signs and symptoms will increase with exercise and during pregnancy.

Diagnosis

- CXR: Left atrial enlargement (early)
- Echocardiogram–most important test in confirming diagnosis
- ECG, CBC, RFT, and electrolytes

Follow-up echocardiography should be done based on the severity of MS

- Mild MS- every 3-5 years
- Moderate MS- every 1-2 years
- Severe MS - yearly

Treatment

- HF- Treatment should be instituted for Acute cases (like pulmonary edema and cardiogenic shock), and symptomatic patients
- For patients with symptoms of congestion- **pulmonary or peripheral edema**
  - ✓ Start **Lasix 40mg po BID and escalate** every 2wks-1 month till symptoms subside.

        - ☛ Maximum daily dose of Lasix is 400mg in 3-4 divided doses.
        - ☛ Look for possible side effects of the drug including hypotension and electrolyte abnormalities
    - ✓ Add **spironolactone 25mgs po/day** in those patients with Cr < 2.5mg/dl and serum $K^+ < 5.5$meq/l
    - ✓ Advise patients to avoid added salt
    - ✓ Once the congestion subsides, reduce Lasix to the lowest possible dose that can control the symptoms
- Patients without congestion but still have **exertional symptoms**
    - ✓ Start **atenolol 25mg po/day and escalate** every 2wks-1month till PR becomes 60-80BPM. Follow for hypotension.
- **Anticoagulation**
    - ✓ **Warfarin 5mg po/**day with target INR 2.0-3.0
        - ☛ Follow with INR every 2 wks initially till the INR stabilizes and then every 1-2months.
        - ☛ Indications include
            - ▪ Prior embolic event, left atrial thrombus and presence of AF
            - ▪ Patients who **cannot afford for follow-up INR** or have higher risk of bleeding- start **aspirin 81mg po/day**
- **Pregnancy**- advise patients to avoid pregnancy and use dual contraception
- **Benzathine penicillin- 1.2 million IU IM every month lifelong** should be given for all CRHD pt's
- **Endocarditis prophylaxis-** not indicated unless there is prior IE episode

- **Indications for surgical intervention**- patients who can afford and have the following indications should be referred as early as possible to undergo PBMV or valve replacement
    - ✓ Moderate to severe MS with symptoms
    - ✓ Asymptomatic patients with moderate to severe MS and either pulmonary artery pressure at rest >50mmHg (can be measured with Doppler echocardiography) or new onset AF

5. Aortic Stenosis (AS)

- ➢ AS occurs in about one-fourth of all patients with chronic VHD
- ➢ ~80% of adult patients with symptomatic, valvular AS are male.
- ➢ It causes obstruction to left ventricular outflow, which results in LVH.
- ➢ When the aortic valve area falls below 1 cm^2, cardiac output fails to increase with exertion, causing angina (but may be normal at rest).

Causes

- Rheumatic fever or RHD.
- Congenital (bicuspid, unicuspid)
    - ○ Calcification of a congenitally abnormal bicuspid/Unicuspid aortic valve.
- Degenerative calcification
    - ○ Calcification of tricuspid aortic valve in elderly.
- Radiation

Clinical Features

Symptoms

- Patients remain asymptomatic till the valve area is ≤ 1 cm^2.
- Classic symptoms include exertional angina, syncope (usually exertional), dyspnea, and excessive fatigue.
- Heart failure symptoms, such as dyspnea on exertion, orthopnea, or PND

Signs

- Active precordium with displaced PMI
- Murmur of AS

Diagnosis

- ✓ CXR findings: Calcific aortic valve, enlarged LV/LA (late)
- ✓ ECG findings: LVH, LA abnormality
- ✓ Echocardiography: Valve lesion, degree of stenosis, LVH
- ✓ Lipid profile
- **Severity**- depends on aortic valve area (AVA)
  - ☛ Mild AS → AVA 1.5-2 cm^2
  - ☛ Moderate AS → AVA 1.0-1.5 cm^2
  - ☛ Severe AS → AVA $\leq$ 1 cm^2
  - ☛ Aortic valve sclerosis- thickened aortic valve with AVA >2 cm^2

Follow-up echocardiography should be done based on the severity of AS

- Mild AS- every 3-5 years
- Moderate AS- every 2 years
- Severe AS - yearly

Treatment

- Mainly indicated for symptomatic patients
- In patients with severe AS (valve area <1 cm2), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage.
- Avoid dehydration and hypovolemia

- ❖ For asymptomatic patients
  - ✓ Prevention of progression of rheumatic AS- **monthly penicillin** prophylaxis
  - ✓ **Hypertension-** should be controlled. Preferably use **ACEIs or CCB, like amlodipine**
  - ✓ Concomitant coronary artery disease (CAD) is common, especially in the elderly. Thus, look for possible evidence of CAD and treat
- ❖ For symptomatic patients- goals include
  - ✓ Treat concurrent cardiovascular conditions, like coronary artery disease
  - ✓ Prevent or treat superimposed diseases that often exacerbate the effects of valve obstruction, like HTN
  - ✓ Maintain optimal loading conditions
  - ✓ Treat symptoms
    - ☛ CHF- start Lasix 40mg po BID/TID and escalate till the congestion improves
    - ☛ Exertional angina and syncope - advice patients to avoid exertion
  - ✓ Patients with depressed EF (LVEF <40%)
  - ✓ Refer to the management of HFrEF guideline and start drugs that have mortality benefits

- Endocarditis prophylaxis- not indicated
- **Indications for surgical intervention-** - patients who can afford and have the following indications should be referred early to undergo **aortic valve replacement**
    - Symptomatic severe AS
    - Severe AS with LVEF <50%
    - Moderate AS with concomitant coronary artery disease requiring bypass graft surgery

Reading assignment

- Tricuspid stenosis (TS)
- Pulmonic stenosis (PS)
- Pulmonic Regurgitation (PR)
- Multiple and Mixed VHD

1.4 Atherosclerotic cardiovascular diseases

1.4.1 Ischemic heart disease (IHD)

- IHD is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium
- Typically occurs when there is imbalance between myocardial oxygen supply and demand
- Commonly caused by atherosclerosis of epicardial coronary arteries
- IHD is the leading cause of death and disability in the developed world
- The prevalence IHD in developing countries is increasing due to urbanization and increased adoption of western type diets

Pathophysiology

- Determinants of myocardial oxygen demand
    - Heart rate
    - Myocardial contractility, and
    - Myocardial wall tension
- Determinants of myocardial oxygen supply
    - Inspired fraction of oxygen
    - Pulmonary function
    - Hemoglobin concentration and function
    - Adequate level of coronary blood flow

☛ Any mismatch between the above factors could result in myocardial ischemia/infarction

Causes

- Atherosclerosis
- Vasospasm (Prinz metal's angina)

- Arterial thrombi
- Coronary emboli
- Aortitis
- Congenital anomalies- the origin of the left anterior descending coronary artery from the pulmonary artery
- Severe anemia or the presence of carboxyhemoglobin
- Increased oxygen demand e.g. - LVH
- Two or more causes of ischemia often coexist in a patient e.g. - LVH due to HTN and atherosclerosis

Coronary atherosclerosis

- Atherosclerosis is the narrowing and stiffening of vessels due to abnormal deposition of atherosclerotic plaque composed of fatty streak, smooth muscle cells, fibroblasts, and intercellular matrix
- When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet the increased myocardial demand
- When the diameter is reduced by ~80%, blood flow at rest may be reduced and symptoms of angina occur at rest
- Clinical manifestations depend on
    - Location of obstruction
    - Severity of obstruction
    - Tempo of onset- acute Vs chronic obstruction

Risk factors for atherosclerosis

- **Nonmodifiable risk factors**
    - Male sex
    - Age: male > 45 yrs, females > 55
    - Family history of premature ischemic heart disease in first degree relative: male < 55 yrs, females < 65
- **Modifiable risk factors**
    - Cigarette smoking
    - HTN
    - DM
    - Dyslipidemia- high LDL and low HDL
    - Obesity
    - Atherogenic diet: high fat diet
    - Alcohol intake
    - Physical inactivity

Spectrum of presentation of IHD

- Asymptomatic
    - Silent myocardial ischemia

- Sudden cardiac death
- Ischemic cardiomyopathy
- **Stable angina pectoris**
- **Acute coronary syndrome (ACS)**
  - Unstable angina (UA)
  - Non-ST segment elevation myocardial infarction (NSTEMI)
  - ST-segment elevation myocardial infarction (STEMI)

Stable angina pectoris

- Due to transient myocardial ischemia
- Characterized by episodes of chest discomfort, usually described as heaviness, pressure, or squeezing with **Levine's sign**
  - ✓ Typically associated with exertion or emotion, and relieved by rest and nitroglycerin
  - ✓ Usually crescendo-decrescendo in nature
  - ✓ Typically lasts 2-5 minutes
  - ✓ Radiates to either shoulder, both arms, back, interscapular region, roof of neck, jaw, teeth, and epigastrium
  - ✓ Rarely localized below the umbilicus or above the mandible and doesn't radiate to the trapezius muscles
- Women, elderly, and diabetic patients can have atypical angina or angina equivalents such as dyspnea, nausea, fatigue, and faintness

Pain characteristics more typical of nonischemic chest discomfort

- Pleuritic pain- sharp or knifelike pain related to respiratory mov't or cough
- Primary or sole location in the mid or lower abdomen
- Any discomfort localized with one finger
- Reproduced by mov't or palpation
- Constant pain lasting for days
- Fleeting pain lasting for seconds or less
- Pain radiating into the lower extremities or above the mandible

Differential Diagnosis for chest pain

1. Heart, pericardium, vascular causes:
   - ❖ Stable angina, variant angina
   - ❖ Acute Coronary Syndrome (ACS)
   - ❖ Pericarditis
   - ❖ Aortic dissection
2. Pulmonary:
   - ❖ Pulmonary embolism
   - ❖ Pneumothorax
   - ❖ Pleuritis (pleural pain)
   - ❖ Pneumonia
   - ❖ Status asthmaticus
3. Gastrointestinal:
   - ❖ Gastroesophageal reflux disease (GERD)

- Peptic ulcer disease (PUD)
- Diffuse esophageal spasm
- Esophageal rupture

4. Chest wall:
    - Costochondritis
    - Muscle strain
    - Rib fracture
    - Herpes zoster
5. Psychiatric:
    - Panic attacks
    - Anxiety
    - Somatization

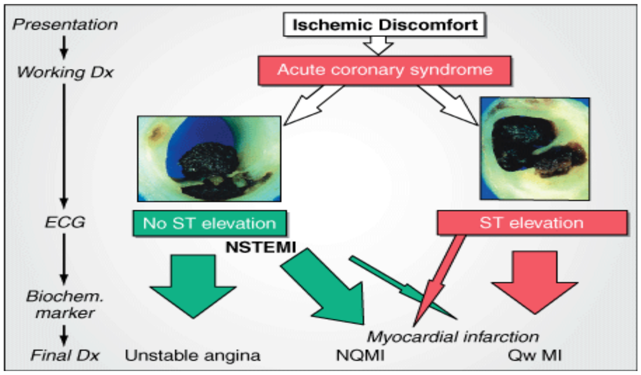
1.4.1.1 Acute coronary syndrome (ACS)

- ACS describes a group of clinical entities that are characterized by severe, acute myocardial ischemia or infarction resulting from thrombotic occlusion of coronary artery/arteries as a result atherosclerotic plaque erosion/rupture.
- Rarely, the ischemia could be due to coronary artery spasm.

CLASSIFICATION OF ACS

ACS comprises the following 3 clinical entities:

1. Unstable angina:
2. ST-segment elevation myocardial infarction (STEMI):
3. Non-ST-segment elevation myocardial infarction (NSTEMI):


Presentation
Working Dx
ECG
Biochem. marker
Final Dx
Ischemic Discomfort
Acute coronary syndrome
No ST elevation
ST elevation
NSTEMI
Unstable angina
Myocardial infarction
NQMI
Qw MI

Figure; Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (*right*) or sub totally occlusive thrombus (*left*). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (*wide red arrow*) ultimately develop a Q wave on the ECG (Qw MI), while a minority (*thin red arrow*) do not develop Q wave and, in older literature, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI) (*wide green arrows*), a distinction that is ultimately made based on the presence or absence of a serum cardiac biomarker such as CK-MB or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q wave on the ECG; a minority develop a Qw MI (*thin green arrow*).

Definitions of ACS

- Combination of symptoms of myocardial ischemia, ECG abnormalities, and rising or falling pattern of cardiac biomarkers
- STEMI- ≥2mm of ST segment elevation in leads V2-V3 and >1mm elevation in the other two contiguous leads
    - ✓ New or presumably new LBBB pattern
- NSTEMI- symptoms of myocardial ischemia and positive cardiac biomarkers

1. Unstable Angina and NSTEMI

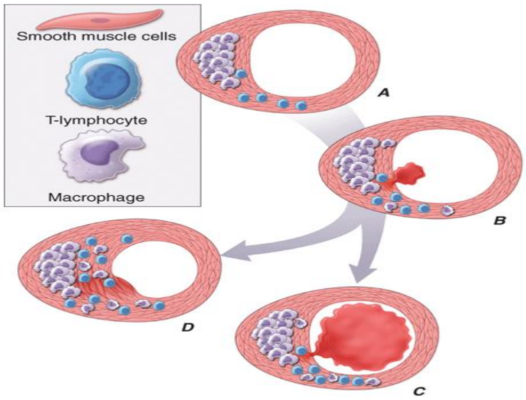
- Unstable angina is considered to be present in the following circumstances:
    - ✓ Angina at rest which is >20 minutes in duration
    - ✓ Severe and New onset angina (within the prior 4-6 weeks)
    - ✓ Increasing angina- increasing frequency, longer in duration, or occurs with less exertion than previous angina (increasing intensity of chest pain).
- Symptoms of myocardial ischemia (typical or atypical) but **no elevation in cardiac enzymes**, with or without ECG changes indicative of ischemia.
- **The distinction between unstable angina and** NSTEMI **is based entirely on cardiac enzymes. The latter** has elevation of troponin or creatine kinase-MB (CK-MB). Both **unstable angina and NSTEMI** lack ST-segment elevations and pathologic Q waves.
- The diagnosis of NSTEMI is established if a patient with clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers
- Unstable angina has a higher risk of MI and death than stable angina, and patients with this diagnosis should be hospitalized.

Pathophysiology

- Four pathophysiologic processes may contribute to the development of UA/NSTEMI
    1. Plaque rupture or erosion with a superimposed nonocclusive thrombus
    2. Dynamic obstruction e.g. vasospasm
    3. Progressive mechanical obstruction

4. Increased myocardial oxygen demand

- More than one of the above processes can be involved
- Patients with UA/NSTEMI frequently have multiple plaques at risk of disruption



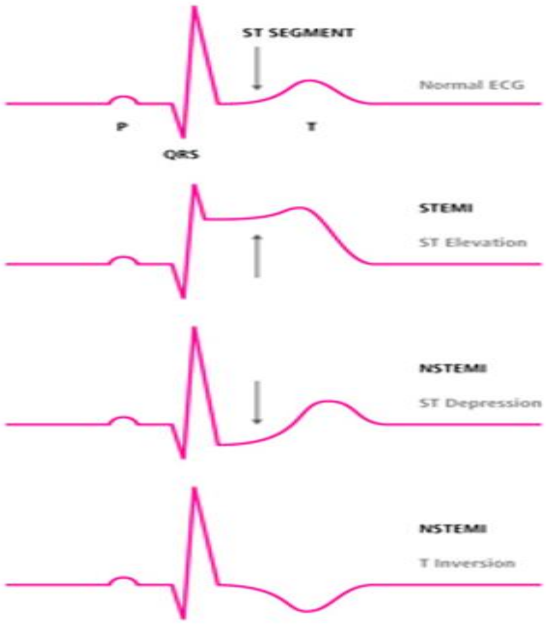
Figure; Plaque rupture, thrombosis, and healing

A. Arterial remodelling during atherogenesis
B. Rupture of the plaque's fibrous cap causes thrombosis.
C. When the clot overwhelms the endogenous fibrinolytic mechanisms, it may propagate and lead to arterial occlusion
D. The subsequent thrombin-induced fibrosis and healing causes a fibroproliferative response that can lead to a more fibrous lesion that can produce an eccentric plaque that causes a hemodynamically significant stenosis.

Diagnosis

- **The diagnosis of UA is based largely on the clinical presentation**
- Perform a diagnostic workup to exclude MI in all patients.
- Patients with unstable angina have a higher risk of adverse events during stress testing. These patients should be stabilized with medical management before referral for stress testing.

- ECG
  - ✓ ST-segment depression
  - ✓ Transient ST-segment elevation
  - ✓ T-wave inversion
- Cardiac biomarkers- elevated in NSTEMI
  - ✓ **Cardiac troponin- more specific and sensitive** marker of myocardial necrosis
  - ✓ CKMB
- Echocardiography
  - ✓ May show regional wall motion abnormalities
- Coronary angiography



2. Acute Myocardial Infarction (STEMI and NSTEMI)

- MI is due to necrosis of myocardium as a result of an interruption of blood supply (after a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis).
- Most cases are due to acute coronary thrombosis: Atheromatous plaque ruptures into the vessel lumen, and thrombus forms on top of this lesion, which causes occlusion of the vessel.

A. **ST-segment elevation myocardial infarction (STEMI)**:
   - ✓ Significant ST elevation or new left bundle branch block (LBBB) on ECG, elevated cardiac enzymes (Troponin and/or CKMB) and symptoms of myocardial ischemia (typical or atypical).

B. **Non-ST-segment elevation myocardial infarction (NSTEMI)**:
   - ✓ No ST elevation on ECG (other ECG evidence of ischemia may or may not be present), elevated cardiac enzymes and symptoms of myocardial ischemia (typical or atypical).

ST-segment elevation myocardial infarction (STEMI)

Clinical Features

- ❖ Up to 50% of cases have precipitating factors(e.g. vigorous physical exercise, emotional stress, or a medical or surgical illness)

- The time of onset of STEMI has a pronounced circadian periodicity, with peak incidence of events between 6 AM and noon
    - ✓ Increase in cathecolamine and cortisol level
    - ✓ Increase in platelet aggregability
- Despite advances in the laboratory detection of STEMI, the patient's history remains crucial to establishing a diagnosis
- **Chest pain**
    - ✓ The pain of STEMI varies in intensity; in most patients it is severe and, in some instances, intolerable
    - ✓ **Patients often describe the pain as heavy, squeezing, and crushing and "an elephant standing on my chest." although occasionally it is described as stabbing or burning**
    - ✓ The duration of the pain is prolonged, usually **lasting > 30 minutes** and frequently for a number of hours
    - ✓ Typically, the pain involves the **central portion of the chest and/or the epigastrium, and on occasion it radiates to the arms.** Less common sites of radiation include the abdomen, back, lower jaw, and neck, commonly to the left side.
    - ✓ The pain may commence when the patient is **at rest**, but when it begins during a period of exertion, it **does not usually subside with cessation of activity**, in contrast to angina pectoris
    - ✓ It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom
- Some patients may have epigastric discomfort.
- Atypical presentations of STEMI include the following:
    - ✓ Heart failure (i.e., dyspnea without pain beginning de novo or worsening of established failure)
    - ✓ Classic angina pectoris without a particularly severe or prolonged episode
    - ✓ Atypical location of the pain
    - ✓ CNS manifestations, resembling those of stroke, secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis
    - ✓ Apprehension and nervousness
    - ✓ Sudden mania or psychosis
    - ✓ Syncope
- **Silent STEMI:** *Can be asymptomatic in up to one-third of patients;* painless infarcts or atypical presentations more likely in postoperative patients, the elderly, diabetic patients, patients without antecedent angina pectoris and women. Sudden cardiac death isn't uncommon
- The prognoses of patients with silent and symptomatic presentations of STEMI appear quite similar
- Angina equivalents- dyspnea, excessive fatigue, diaphoresis, indigestion should raise the suspicion of ACS in these patients

P/E

- Anxious, restless and may be in cardiopulmonary distress
- Heart rate can vary from a marked bradycardia to a rapid regular or irregular tachycardia
- Mostly normotensive
- Fever
- Bilateral basal rales
- Raised JVP
- Quiet precordium, and the AI may be difficult to palpate
- S3 and S4 gallop
- Murmur of MR and friction rub

☛ N.B. Right ventricular infarct will present with inferior ECG changes, hypotension, elevated jugular venous pressure, hepatomegaly, and clear lungs.

Killip classification of acute MI

- Class I - no evidence of HF
- Class II - findings consistent with mild to moderate HF (S3, lung rales less than one-half way up the posterior lung fields, or jugular venous distension)
- Class III - overt pulmonary edema (click and see 1.10.2 Pulmonary edema)
- Class IV - Cardiogenic shock (pump failure) *(click and see the respective topic)*

Diagnosis of STEMI

- ECG: Markers for ischemia/infarction include:
    - **ST-segment elevation:** indicates transmural injury and can be diagnostic of an acute infarct.
    - **ST-segment depression:** Subendocardial injury
    - **T-wave inversion** is sensitive but not specific
    - **Peaked T waves:** Occur very early and may be missed
    - **Q waves:** Evidence for necrosis (specific).
- Cardiac enzymes: currently the diagnostic gold standard for myocardial injury
    - Troponins (Troponin I and T): most important enzyme test to order
    - CK-MB: less commonly used
    - Cardiac enzymes are drawn serially: once on admission and every 6 hours until three samples are obtained. The higher the peak and the longer enzyme levels remain elevated, the more severe the myocardial injury and the worse the prognosis.

Other IX

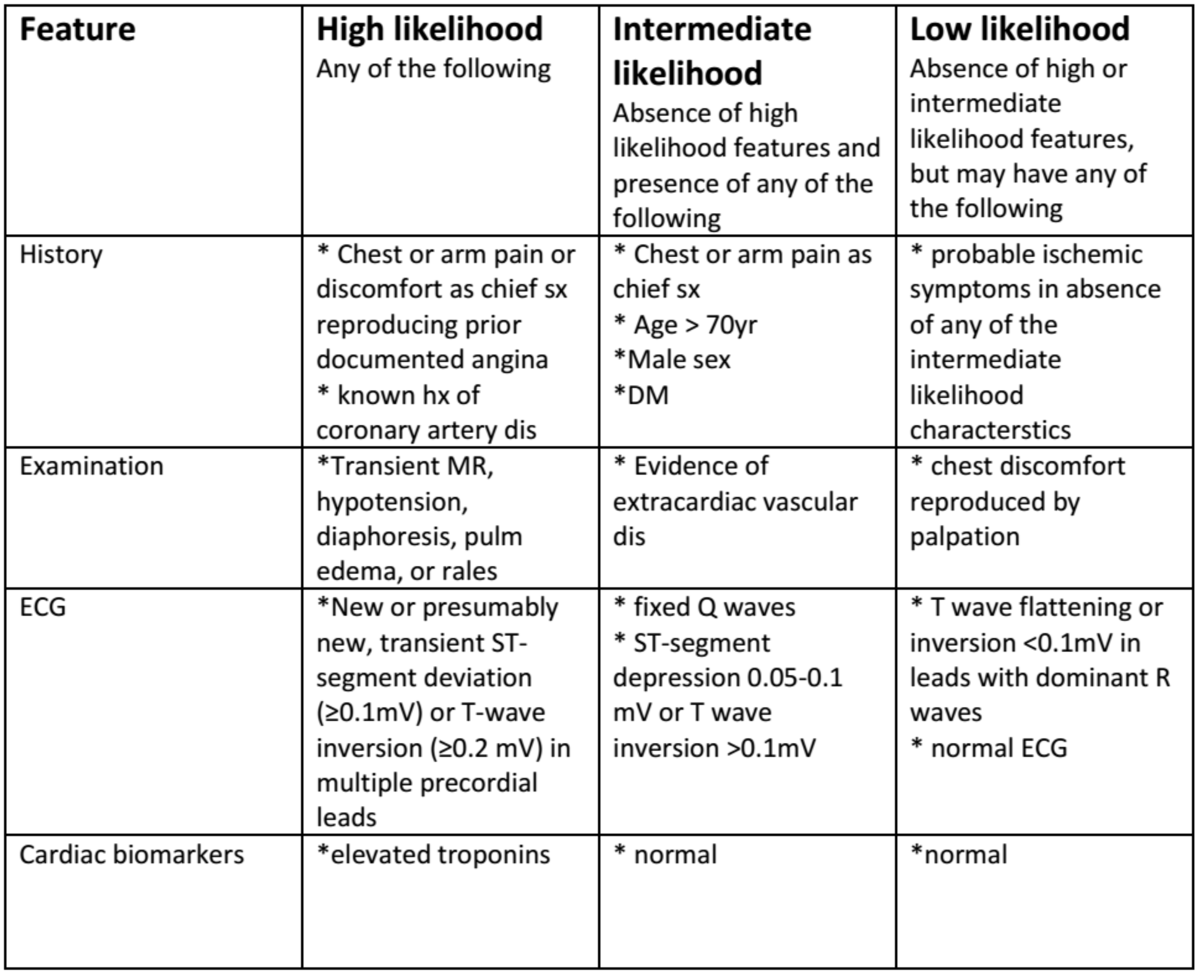
- ✓ Cardiac imaging: **ECHO,** Cardiac MRI and angiography, *radionuclide imaging* *techniques*

- ✓ CBC with platelet count
- ✓ PT, aPTT and INR
- ✓ Electrolytes
- ✓ BUN & Creatinine
- ✓ RBS
- ✓ Serum lipid profile
- ✓ Non specific indices of tissue necrosis and inflammation

COMPLICATIONS OF STEMI

- Mechanical
    - Rupture of the left ventricular free wall
    - Rupture of IVS
    - MR
    - Left ventricular dysfunction
    - LV aneurysm
    - Pericarditis
- Electrical complications
    - Arrhythmias
- Complications which can be as a result of both mechanical and electrical disturbances
    - Heart failure
    - Cardiogenic shock
    - Thromboembolism

Likelihood that signs and symptoms represent an ACS



Feature	**High likelihood** Any of the following	**Intermediate likelihood** Absence of high likelihood features and presence of any of the following	**Low likelihood** Absence of high or intermediate likelihood features, but may have any of the following
History	* Chest or arm pain or discomfort as chief sx reproducing prior documented angina * known hx of coronary artery dis	* Chest or arm pain as chief sx * Age > 70yr *Male sex *DM	* probable ischemic symptoms in absence of any of the intermediate likelihood characterstics
Examination	*Transient MR, hypotension, diaphoresis, pulm edema, or rales	* Evidence of extracardiac vascular dis	* chest discomfort reproduced by palpation
ECG	*New or presumably new, transient ST-segment deviation (≥0.1mV) or T-wave inversion (≥0.2 mV) in multiple precordial leads	* fixed Q waves * ST-segment depression 0.05-0.1 mV or T wave inversion >0.1mV	* T wave flattening or inversion <0.1mV in leads with dominant R waves * normal ECG
Cardiac biomarkers	*elevated troponins	* normal	*normal

Management of ACS

- **Early referral to the high-level facility or urgent specialist consultation is recommended**

Approach to Treating a Patient with Chest Pain

- Rule out any life-threatening causes. These include
  - ✓ ACS
  - ✓ Aortic dissection
  - ✓ Pericarditis with cardiac tamponade
  - ✓ Pulmonary embolus
  - ✓ Tension pneumothorax
  - ✓ Esophageal rupture
- Assess vital signs
- Develop a focused history and P/E
- Investigation: focused
  - ✓ ECG in almost all cases

- ✓ Cardiac enzymes (CK, CK-MB, troponin) depending on clinical suspicion
- ✓ CXR in a supportive clinical data
- ✓ Under appropriate clinical setting, work up the patient for pulmonary embolism (PE)

Non pharmacologic

- Categorize patients based on the above evaluation (see the above table)
  - ✓ Patients with **high and intermediate likelihood of ACS should be admitted to the medical ICU** and managed according to ACS management protocol
  - ✓ Patients with low likelihood of ACS can be discharged from the ED with advice to come early if they have similar chest pain
    - ☛ Manage the possible cause of the current complaint
- Hospital admission and **strict bed rest** with continuous cardiac monitoring (ECG monitoring).
  - ❖ Absolute bed rest for 12hrs
  - ❖ Movement only around the bed after 48hrs
  - ❖ Movement to toilet and less than ordinary activities after 72hrs
  - ❖ Avoid strenuous activities for 2 weeks
- Establish IV access and obtain blood for troponin, electrolytes, coagulation profile, RFT.
- NPO and fluid diet for the 1st 12hr's
- Give supplemental oxygen if patients are hypoxic (Spo_2 <90 %).

Pharmacologic

- **Glucose and electrolytes**
  - ➢ keep RBS level b/n 140-180 mg/dl (use the protocol for management of blood glucose in critical patients)
  - ➢ keep serum K+ level > 4 meq/l
- **Provide pain control:**
  - ○ **Nitroglycerin:** short acting **(sublingual or spray):**
    - ▪ **3 doses** of sublingual nitroglycerine **(0.4 mg)** for persistent chest pain **every 5 minutes** if no hypotension or RV infarction
    - ▪ Patients should be advised to take 1 dose promptly in response to chest pain. If pain is unrelieved or worsened 3 to 5 minutes after 1 dose, call cardiac emergency team immediately
    - ▪ Don't give nitrates for patients who took phosphodiesterase inhibitors (sildenafil)
  - ○ **Morphine** 2 - 5 mg IV every 5-15 min if pain refractory to nitrate therapy alone. (C/I: hypotension) then 5mg, IV, QID and PRN
    - ✓ **Alternative; pethidine** 25-50 mg IV as needed weaker than morphine
  - ○ For patients with continuous or recurrent chest pain despite the above treatment, **IV nitroglycerine** infusion should be given in the absence

of contraindications

    - 5 µg/minute, increase by 5 µg/minute every 3 to 5 minutes to 20 µg/minute. If no response at 20 µg/minute, may increase by 10 to 20 µg/minute every 3 to 5 minutes (maximum dose: 400 µg/minute)

- **Dual antiplatelet therapy**:
  - ✓ **ASA 325 mg** loading (Advice to chew the tablet right away) followed by 81-100 mg (usually **81mg**) Po daily lifelong (commonly used in our setup) PLUS
  - ✓ **Clopidogrel**
    - ○ *UA/NSTEMI:*
      - Initial: 300 mg or 600 mg loading dose, followed by 75 mg once daily for up to 12 months in combination with aspirin, followed by aspirin indefinitely
    - ○ *STEMI receiving fibrinolytic therapy (in combination with aspirin and appropriate anticoagulant)*
      - Age ≤75 years: Loading dose of 300 mg followed by 75 mg once daily for at least 14 days up to 1 year (in the absence of bleeding).
      - Age >75 years: 75 mg once daily (no loading dose) for at least 14 days up to 1 year (in the absence of bleeding).
- **β-Blockers:**
  - ○ Beta-blockers should be initiated within the first 24 hours post myocardial infarction and continued indefinitely for most patients
  - ✓ Metoprolol; Metoprolol tartrate is short acting form, which is preferred as initial management for ACS. Metoprolol succinate is long acting form
    - ☛ ***Metoprolol tartrate*** *(Immediate release):* 50 mg, PO, BID; usual dosage range: 50 to 200 mg, PO, BID; may increase dose at weekly intervals to desired effect (maximum: 400 mg/day).
    - ☛ ***Metoprolol succinate*** *(Extended release):* Initial: 100 mg, PO, daily; may increase dose at weekly intervals to desired effect (maximum: 400 mg/day).
  - ✓ **Alternative; atenolol** 25 - 50mg, PO, BID

  - ❖ Beta blockers should be escalated if no heart failure, hypotension, bradycardia, or active obstructive air way disease
  - ❖ If β-Blockers are C/I due to obstructive airway disease use Verapamil 80-120 mg, PO, TID
  - ❖ β-Blockers have cardiac remodeling effect

- Anticoagulation using Heparin (duration of therapy is for 5-7 days until ambulation starts)

- ✓ **Enoxaparin**
  - ○ *Patients <75 years of age:* Initial: 30 mg IV single bolus plus 1 mg/kg (maximum: 100 mg for the first 2 doses only) SC, BID.
    - ▪ The first SC dose should be administered with the IV bolus. **Maintenance: After first 2 doses, administer 1 mg/kg Sc, BID**
  - ○ *Patients ≥75 years of age:* Initial: 0.75 mg/kg, SC, BID (**Note:** No IV bolus is administered in this population); a maximum dose of 75 mg is recommended for the first 2 doses.
    - ▪ **Maintenance: After first 2 doses, administer 0.75 mg/kg SC, BID**
- ✓ **Alternative: UFH** 5000 IU (60 IU/kg), IV loading followed by 250 IU/kg (17,500 IU), SC BID
  - ☛ If infuser is available give maintenance dose 12U/Kg/hr IV continuous infusion.

- Other therapies
  - a. **Statin**
    - ❖ High intensity statin therapy; for *Age ≤ 75* years
      - ✓ **Atorvastatin** 80 mg PO daily; if unable to tolerate, may reduce dose to 40 mg once daily
      - ✓ Alternative; rosuvastatin 20 to 40mg PO, daily
    - ❖ Moderate-intensity statin therapy; for age > 75 years *or not a candidate for high intensity therapy*
      - ✓ Atorvastatin 10 to 20 mg PO daily
      - ✓ Alternative;
        - ○ Rosuvastatin 20 to 40mg PO, daily or
        - ○ Simvastatin 20 to 40mg PO, daily
    - ▪ Low intensity is used to decrease statin induced myopathy in old age

  - b. **ACEIs** in the absence of C/I or **ARBs** in ACEI intolerant
    - ✓ ACEIs
      - ○ **Note:** In those patients with STEMI in the anterior location, heart failure, or LV ejection fraction ≤ 0.4, an ACE inhibitor (eg, captopril) should be initiated within the first 24 hours after MI

      - ○ **Enalapril** 2.5 mg, PO, BID titrated as tolerated to target dose of 10 mg, PO, BID (maximum: 20 mg/day) or
      - ○ **Captopril** Initial: 6.25 mg; if tolerated, follow with 12.5 mg, PO, TID; then increase to 25 mg, PO, TID during next several days and then gradually increase over next several weeks to target dose of 50 mg, PO, TID
        - ▪ some dose schedules are more aggressive to achieve an increased goal dose within the first

few days of initiation.

- ✓ ARBs
    - Candesartan 4mg BID escalated
    - **Note:** Concurrent therapy with an ACE inhibitor may provide additional benefit in patients with HF with reduced EF who remain symptomatic on standard therapy and are unable to receive an aldosterone antagonist

c. Aldosterone antagonists for those with LV EF < 40%, are already on ACE - I and either HF or DM in absence of hyperkalemia and renal failure

- **Spironolactone**, 12.5 to 25 mg, PO, daily; maximum: 50 mg/day
- **Note:** withhold treatment if potassium >5.5 mEq/L or renal function worsens (serum creatinine >4 mg/dL); hold doses until potassium is <5 mEq/L and consider restarting with a reduced dose after confirming resolution of hyperkalemia/renal insufficiency for at least 72 hours

d. Oral anticoagulation(**warfarin)** for those at high risk of thromboembolization

- ☛ **Atrial fibrillation with CHA$_2$DS$_2$- VASc > 1**, LV thrombus
- ☛ Considered in patients with poor LV function and apical hypokinesis
- ☛ **Warfarin; Start 2 to 5 mg, PO, daily for 2 days; lower doses (e.g. 5 mg once daily)**

- **For CHA$_2$DS$_2$- VASc and HAS-BLED score in patients with atrial fibrillation, supratherapeutic INR (Management of warfarin-associated bleeding) click here → Arrhythmia**

e. GI prophylaxis and bowel care:

- **Omeprazole** 20 mg po BID routine and
- Laxatives for constipation
    - **Bisacodyl** 5 to 15 mg, PO, daily **or**
    - **Lactulose, 15 to 30 mL** (10 to 20 g or 1 to 2 packets), PO, daily; may increase to 60 mL (40 g or 2 to 4 packets) daily if necessary

- Follow up (**Cardiac Monitoring for a Patient with an Acute MI)**
    - ➢ BP and PR
    - ➢ Rhythm strip with continuous cardiac monitor: Watch for arrhythmias.
    - ➢ Auscultate the heart (S$_3$ & S$_4$ gallops, friction rub, and so on) and lungs (crackles may indicate LV failure, pulmonary edema).
    - ➢ Follow for chest pain or angina equivalent symptoms
    - ➢ Take ECG every day for at least 3 days→ evolutionary changes (degree

- of ST elevation, Q waves)
- Echocardiography: LV function, wall motion abnormality, LV thrombus
- Follow troponin levels
- Watch for mechanical and electrical complications **(the most feared cxn of ACS is arrythmia)**
- Watch for bleeding in patients at high risk for bleeding

- Preparation for discharge
  - Ambulation: hemodynamically stable and no chest pain for 12-24 hrs
  - Discharge after a minimum of 5 days of admission can be considered if
    - ✓ Pt is hemodynamically stable and no signs of mechanical or electrical complications
    - ✓ No sign of ongoing ischemia (no chest pain, new ECG changes and troponin level decreasing)
    - ✓ Pt is able to ambulate without symptoms
- Long term medications
  - ASA, B blockers, ACEIs/ARBs, aldosterone antagonists, and statin should be continued lifelong
  - Clopidogrel should be continued for a minimum of 1 month and ideally up to 1 year
- Risk factor modification:
  - Optimal treatment of HTN, DM, dyslipidemia, smoking cessation
- Return to activities
  - Most patients with uncomplicated course can return to activities after 2 weeks (avoid strenuous activities including coitus for 2 weeks)
  - Should be advised to slowly increase the level of exertion watching for symptoms (e.g. Walking distance)
- Finally, all patients who can afford, the option of getting referred to a cardiac hospital in A.A. for risk stratification with stress ECG and diagnostic and therapeutic coronary intervention should be given. Hemodynamically stable patients with no ongoing or recurrent ischemia who are on appropriate medications can fly with reasonable safety after 2 weeks.
  NB. Consult the appropriate risk stratification models for prognostication

1.4.1.2 Chronic coronary syndrome

- Chronic Coronary Syndrome is usually due to atherosclerotic lesions that narrow the major coronary arteries.
- Coronary ischemia is due to an imbalance between blood supply and oxygen demand, leading to inadequate perfusion.
- Stable angina occurs when oxygen demand exceeds available blood supply.

Major risk factors

- DM – worst risk factor
- Hyperlipidemia – elevated LDL
- HTN – most common risk factor
- Cigarette smoking
- Age (men >45 years; women >55 years)
- Family history of premature CAD or MI in first-degree relative: Men <55 years; women <65 years
- Low levels of HDL

Less common risk factors include:

- End-stage renal disease (ESRD) on hemodialysis,
- HIV infection,
- History of mediastinal radiation.

Minor risk factors (less clear significance) include:

- Obesity
- Sedentary lifestyle (lack of physical activity)
- Stress
- Excess alcohol use

Clinical Features

- Chest pain or substernal pressure sensation
  - ✓ Lasts less than 10 to 15 minutes (usually 1 to 5 minutes).
  - ✓ Frightening chest discomfort, usually described as heaviness, pressure. squeezing, tightness; rarely described as sharp or stabbing pain.
  - ✓ Pain is often gradual in onset.
  - ✓ Brought on by factors that increase myocardial oxygen demand, such as exertion, stress, or drugs.
  - ✓ Relieved with rest or nitroglycerin

Diagnosis and investigation

- ❖ Note that physical examination in most patients with CCS is normal.
- ❖ Resting ECG:
  - ✓ Usually normal in patients with chronic coronary syndrome
  - ✓ Q waves are consistent with a prior MI
  - ✓ If ST-segment or T-wave abnormalities are present during an episode of chest pain, then treat as unstable angina.
- ❖ Stress test:
  - ✓ Useful for patients with an intermediate pretest probability of CAD based upon age, gender, and symptoms.
  - ✓ Stress testing is used in the following situations:
    - ☛ To confirm diagnosis of angina
    - ☛ To evaluate response to therapy in patients with documented CCS
    - ☛ To identify patients with CCS who may have a high risk of acute coronary events

Treatment of CCS

- Risk factor modification
    - Smoking cessation
    - Blood pressure control
    - Dyslipidemia management:
    - Obesity: weight loss modifies other risk factors (diabetes, HTN, and hyperlipidemia) and provides other health benefits.
    - Exercise: it minimizes emotional stress, promotes weight loss, and helps reduce other risk factors.
    - Diet: Reduce intake of saturated fat and cholesterol

Standard of care for patients with CCS

- Antiplatelet therapy
    - ASA 75-100 mg PO daily
    - Alternative: Clopidogrel 75 mg Po daily
- Beta blocker: chest pain, heart rate and blood pressure control
    - Metoprolol succinate 50-200 mg PO daily
    - Alternative: Bisoprolol 2.5-10 mg PO daily
- Statin: target LDL< 70 mg/dl, dose of statin titrated as per the response
    - Atorvastatin 20-80 mg PO daily
    - Alternative: Rosuvastatin 5-20 mg PO daily
- **Angina management**
    - Betablockers: see above
    - Calcium channel blockers
        - Amlodipine 2.5-10 mg PO daily for those with hypertension
    - Nitrates
        - Nitroglycerine 0.4 mg sublingual tablets for acute relief
        - Isosorbide dinitrate 2.5-20 mg PO single dose or divided doses as needed
        - Trimetazidine 35 mg Po daily
- Review risk factor, symptoms and indication for revascularization
- Refractory cases: Need Cardiologist evaluation

Coronary revascularization

- Indications
    - The presence of unstable phases of the disease
    - Intractable symptoms despite medical therapy
    - Severe ischemia or high-risk coronary anatomy
    - Diabetes
    - Impaired LV function
- Revascularization should be employed in conjunction with but not replace the continuing need to modify risk factors and assess medical therapy
- Two options
    - Percutaneous coronary intervention (PCI)
    - Coronary artery bypass grafting (CABG)
- Indications for early revascularization
    - Recurrent angina at rest despite medical Rx
    - Elevated troponin

- ✓ New ST-segment depression
- ✓ Recurrent angina/ischemia with CHF symptoms
- ✓ Positive stress test
- ✓ EF < 40 %
- ✓ Decreased BP
- ✓ Sustained VT
- ✓ PCI < 6 months, prior CABG
- ✓ Multiple risk factors

- Revascularization should be combined with medical therapy

What is anterior MI, Inferior MI and posterior MI?
→refer under short case of Nitsbin (click here → Chapter 6; Basics of ECG and ECG interpretation, Myocardial Ischemia/infarction)

1.4.2 Peripheral Arterial Disease (Chronic Arterial Insufficiency)

- Peripheral arterial disease (PAD) is an occlusive atherosclerotic disease of the lower extremities.
  - ➢ Narrowing of arteries other than those supplying heart (CAD) and Brain (CVA)
  - ➢ It is an arterial ulcer which commonly affect legs
- Patients with PAD usually have coexisting CAD (with CHF, history of MI, and so on) and other chronic medical problems (e.g., diabetes, lung disease)
- Sites of occlusion/stenosis:
  - ○ Superficial femoral artery (in Hunter canal) is the most common site
  - ○ Popliteal artery
  - ○ Aortoiliac occlusive disease

Risk factors

- ➢ Smoking is by far the most important risk factor
- ➢ Chronic Coronary Syndrome
- ➢ Dyslipidemia
- ➢ Hypertension
- ➢ Diabetes: prevalence is markedly increased in these patients
- ➢ Age > 65

Clinical Features

Symptoms:

- **Intermittent claudication**: Cramping leg pain that is reliably reproduced by same walking distance (distance is very constant and reproducible). Pain is completely relieved by rest.
- **Rest pain (continuous):** Usually felt over the distal metatarsals, where the arteries are the smallest. Often prominent at night *(awakens patient from sleep).* Hanging the foot over side of the bed or standing relieves pain (extra perfusion to ischemic areas due to gravity)
    - Rest pain is always worrisome: suggests severe ischemia (**Critical limb ischemia**) such that frank gangrene of involved limb may occur in the absence of intervention.

Signs:

- Diminished or absent pulses, muscular atrophy, decreased hair growth, thick toenails, and decreased skin temperature
- Ischemic ulceration (usually on the toes)
- Cold skin
- Localized skin necrosis: Secondary to local trauma that does not heal (due to ischemic limb)
- Tissue infarction/gangrene in end-stage disease
    - Bluish skin discoloration which complicate with tissue death and Amputation
- Pallor of elevation and rubor of dependency (in advanced disease)
    - Burger sign +ve → pallor on elevation of limb and redness while changing to resting position

- Femoral or popliteal disease causes calf claudication.
- Aortoiliac occlusive disease causes buttock and hip claudication (in addition to the calves).

Rutherford and Fontaine symptom classification systems

Rutherford

- Stage Zero (0) → Asymptomatic
- Stage 1 → mild claudication, claudication distance > 200 meter
- Stage 2 → moderate claudication, claudication distance < 200 meter
- Stage 3 → severe claudication.
- Stage 4 → rest pain
- Stage 5 → minor tissue loss with ischemic nonhealing ulcer or focal gangrene with diffuse pedal ischemia
- Stage 6 → major tissue loss, frank gangrene extending above trans metatarsal level, functional foot no longer salvageable

Fontaine

- Stage 1 — No symptoms
- Stage 2 — Intermittent claudication subdivided into:
  - Stage 2a — Without pain on resting, but with claudication at a distance of greater than 650 feet (200 meters)
  - Stage 2b — Without pain on resting, but with a claudication distance of less than 650 feet (200 meters)
- Stage 3 — Nocturnal and/or resting pain
- Stage 4 — Necrosis (death of tissue) and/or gangrene in the limb

Diagnosis

- Clinical suspicion based on symptoms, signs and risk factors
- Ankle-to-brachial index (ABI): Ratio of the systolic BP at the ankle to the systolic BP at the arm.
  - Normal $\mathbf{ABI} = \frac{\textbf{SBP of ankle}}{\textbf{SBP OF Brackial artery}} = \mathbf{0.9 - 1.3}$
  - SBP of ankle measured by Doppler ultrasound guided BP measurement. But, SBP of arm can be measured by sphygmomanometer (by any BP cuff available in the ward)
  - ABI < 0.9 is evidence for PAD, ABI >1.3 is due to no compressible vessels (vessel wall calcification) and indicates severe disease
  - Claudication usually when ABI < 0.7
  - Rest pain usually when ABI < 0.4
- Doppler study of the peripheral vessels
- Arteriography (contrast in vessels and radiographs)
  - Gold standard for diagnosing and locating PAD

Treatment

Non pharmacologic

Conservative management for intermittent claudication.

- **Smoking cessation (the importance of this cannot be overemphasized).** Smoking is linked to progression of atherosclerosis and causes vasoconstriction (further decreasing blood flow).
- Graduated exercise program: Walk to point of claudication, rest, and then continue walking for another cycle.
- Foot care (especially important in diabetic patients).
- Avoid extremes of temperature (especially extreme cold).

Pharmacologic

- Atherosclerotic risk factor reduction (control of hyperlipidemia, Hypertension, Diabetes):

- Antiplatelets
    - ASA 81-100 mg Po daily
    - Alternative: Clopidogrel 75 mg Po daily
- Statin
    - Atorvastatin 20 - 80 mg Po daily
    - Alternative: Rosuvastatin 5-20 mg Po daily

1.4.3 Arterial occlusion (acute limb ischemia)

- Acute occlusion of an artery, usually caused by embolization.
- Common femoral artery is the most common site of occlusion.
- Less commonly, in situ thrombosis is the cause.

Sources of emboli:

- Heart (85%)
    - Atrial fibrillation is the most common cause of embolus from the heart
    - Post-MI
    - Post arterial procedure (i.e., coronary angiogram, peripheral angiogram)
    - Endocarditis
    - Myxoma
- Aneurysms
- Atheromatous plaque

Clinical Features of Acute Limb Ischemia (Remember the 6 Ps)

- **P**ain: acute onset. The patient can tell you precisely when and where it happened. The pain is very severe, and the patient may have to sit down or may fall to the ground.
- **P**allor
- **P**olar (cold)
- **P**aralysis
- **P**aresthesia's
- **P**ulselessness

Diagnosis

- Clinical: high index of suspicion with supportive clinical data.
- **Doppler study of the vessels.**
- ECG to look for MI, AFib
- Echocardiogram for evaluation of cardiac source of emboli–valves, thrombus, shunt

Treatment

- Main goal: Assess viability of tissues to salvage the limb.
- Skeletal muscle can tolerate 6 hours of ischemia; perfusion should be re-established within this time frame.
- Supportive management
  - Immediately anticoagulate with IV heparin.
  - Strong analgesic like morphine for pain
  - Positioning and psychological support
- **Definitive mgt**
  - bypass versus angioplasty in severe ischemia of the leg (BASIL) trial
  - Percutaneous intervention (angioplasty, stent) is a less invasive alternative to surgery
  - Catheter-based intra-arterial thrombolytic therapy is an alternative to surgery or percutaneous intervention
  - **Urgent referral to the facility where reperfusion is available in consultation with specialist.**

1.5 Hypertension (የደም ግፊት) and HHD

Hypertension

- Hypertension is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases.
- According to the WHO STEPS survey the prevalence of hypertension in Ethiopia is 16%.
- In Ethiopia and other low- and middle-income countries, there is a wide gap between evidence- based recommendations and current practice.
- Treatment of major CVD risk factors remains suboptimal, and only a minority of patients who are treated reach their target levels for blood pressure, blood sugar and blood cholesterol.

When to measure blood pressure

- Measuring blood pressure is the only way to diagnose hypertension, as most people with raised blood pressure have no symptoms.
- Blood pressure measurements should be conducted on all patients during health facility visits as part of the vital sign.
- Every patient with elevated blood pressure readings requires immediate follow-up, according to the protocol.
- More frequent blood pressure measurements and control is particularly important in adults who:
  - Have had a prior heart attack or stroke

- ✓ Have diabetes
- ✓ Have chronic kidney disease (CKD)
- ✓ Are obese
- ✓ Use tobacco
- ✓ Have a family history of heart attack or stroke

How to measure blood pressure

- ❖ Effective treatment algorithms for hypertension are dependent on accurate blood pressure measurement.
- ❖ The following advice should be followed for measuring blood pressure:
  - ✓ Use the **appropriate cuff size,** noting the lines on the cuff to ensure that it is positioned correctly on the arm. (If the arm circumference is >32 cm, use large cuff.)
    - ➢ The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference
  - ✓ On initial evaluation it is preferable to measure blood pressure on **both arms** and use the arm with the **higher reading** thereafter
  - ✓ The patient should be sitting with back supported, legs uncrossed, empty bladder, relaxed for 5 minutes and not talking.
  - ✓ No caffeine during the hour preceding the reading and no smoking during the preceding 30 minutes
  - ✓ No exogenous adrenergic stimulants, such as phenylephrine in decongestants or eye drops for pupillary dilatation
  - ✓ Take **at least two readings** on each visit, separated by as much time as possible; if readings vary by more than 5 mmHg, take additional reading until two consecutive readings are close
  - ✓ **For the diagnosis of hypertension, take measurement on at least two visits ≥ one week apart**
  - ✓ Check for postural changes by taking readings after five minutes supine, then immediately and two minutes after standing - this is particularly important in patients over age 65, diabetics, or those taking antihypertensive drugs
  - ✓ Blood pressure can be measured either by a conventional sphygmomanometer, using a stethoscope, or by an automated electronic device. The WHO recommended calibrated electronic device, if available, is preferred because it provides more reproducible results and is not influenced by variations in technique or by the bias of the observers.

Diagnosing hypertension

- ❖ The diagnosis of hypertension should be confirmed at an additional patient visit, usually 1 to 4 weeks after the first measurement depending on the measured values and other circumstances.
- ❖ In general, hypertension is diagnosed if, on two visits, on different days:
  - ✓ Systolic blood pressure on both days is ≥140 mmHg and/or diastolic blood pressure on both days is ≥90 mmHg.

Diagnosis of hypertension			
Previously		Currently	
Stage	Value	Stage	Value
Normal	<120/80 mmHg	Normal	<120/80 mmHg
Pre hypertension	$\frac{120-139}{80-89}$	Elevated	$\frac{120-129}{<80}$
Stage I HTN	$\frac{140-159}{90-99}$	Stage I HTN	$\frac{130-139}{80-89}$
Stage II HTN	$\frac{160-179}{100-109}$	Stage II HTN	≥140/90 mmHg
Hypertensive urgency	≥180/110 mmHg		
Hypertensive emergency	≥180/110 mmHg with end organ damage		
Isolated systolic hypertension	≥140/ <90		
In our setup we are still using the previous staging system for clinical purpose			

Clinical Condition	**Office Blood Pressure Measurement**			
	< 140/90	140-159/90-99	160-179/100-109	≥180/110
If there is no evidence of end-organ damages	Re-measure after 1year	Confirm in one Month	Confirm as soon as possible within one week	Diagnose HTN and refer to specialist

If there is evidence of end-organ damages	Confirm HTN and refer to specialist
Hypertensive Crises (BP> 180/110 mmHg) with or without target organ damage	

Once diagnosis of hypertension is made: **Look for end-organ damage based on:**

- **History**: Symptoms of heart failure (SOB, unusual fatigue and body swelling), history of sudden onset body weakness (stroke), intermittent claudication or previous diagnosis of the above problems on previous evaluation at other health institutions, severe headache and blurring of vision.
- **Physical Examination**: Pulse rate and rhythm, signs of heart failure (edema, elevated JVP, crackles on the lungs), Focal neurologic deficit, eye signs. The physical examination should be done to the maximum capacity of the health work force including fundoscopic retinal examination if possible.
- **Laboratory and other diagnostic tests**:
  Health facilities should thrive to avail at east mandatory tests. Please note that waiting for laboratory tests shouldn't delay the intervention of hypertension as the disease do much harm than the extra benefit obtained from the tests. The tests are categorized as follows:
  - ✓ **Mandatory tests at diagnosis** (urine dipstick to check for protein, Creatinine to check for renal function)
  - ✓ **Optional tests at diagnosis** (ECG to look for effect of blood pressure on the heart, Serum electrolytes mainly potassium, TFT to assess a secondary cause of hypertension)
  - ✓ **Indication based tests** (Echocardiography for heart failure patients, brain imaging for suspicion of stroke)
  - ✓ **Comorbidity and risk factor assessment tests** (Blood sugar and cholesterol)
- **Look for risk factors:**

- History: Smoking, excess salt intake, sedentary life, low fruit and vegetable intake, excess alcohol consumption

- Physical Measurement: Weight, height, abdominal circumference, Calculate BMI:

- Cardiovascular Risk assessment; For all patients found to have raised BP, their future 10-year cardiovascular risk should be assessed by using WHO CV risk score (Refer WHO CV risk assessment manual). In a setting where serum cholesterol and FBS can be determined use the laboratory-based risk assessment. If laboratory assessment service is not available, the non-laboratory-based risk chart.

Classification of HTN

1. **Essential or primary HTN:**

- ❖ A multi factorial disease where no single etiology is identified
- ❖ Is the commonest type of HTN accounting for 90 — 95 % of the cases
- ❖ It results from the interaction between genetic predisposition and environmental factors

2. **Secondary HTN**

- ❖ Occurs secondary to an identifiable cause
- ❖ Accounts for 5 — 10 % of the cases
  - ✓ Renal paranchymal disease
  - ✓ Renovascular hypertension : renal artery stenosis
  - ✓ Primary aldosteronism
  - ✓ Cushing’s syndrome
  - ✓ Pheochromocytoma

RISK FACTORS FOR ESSENTIAL HYPERTENSION

- ❖ Family histroy of hypertension
- ❖ Black race
- ❖ Increased sodium intake
- ❖ Excess alcohol intake
- ❖ Cigarette smoking
- ❖ Obesity
- ❖ Dyslipidemia
- ❖ Certain personality traits, such as hostile attitudes and time urgency/impatience
- ❖ Pregnancy

Indications for Work-up for Secondary Hypertension

1. Severe or resistant hypertension
2. An acute rise in blood pressure developing in a patient with previously stable values
3. Age less than 30 years in non-obese, non-black patients with a negative family history of and no other risk factors (e.g., obesity) for hypertension
4. Malignant or accelerated hypertension
5. Proven age of onset before puberty

Hypertension based on ambulatory BP monitoring

- ✓ A 24 hr mean of ≥ 125/75 mmHg

- ✓ Day time (awake) mean of ≥ 130/80 mmHg
- ✓ Night time (asleep) mean of ≥ 110/65 mmHg

White coat HTN: is defined as BP that is consistently elevated by office reading only.

Hypertension Treatment

Who should receive hypertension treatment?

- ➢ Hypertension treatment is indicated for adults diagnosed with hypertension, as defined above (SBP ≥140 mmHg and/or DBP ≥90 mmHg).
- ➢ Patients with SBP ≥180 mmHg or DBP ≥110 mmHg may be indicated for immediate treatment based on one assessment.
- ➢ Lifestyle counseling (healthy diet, physical activity, Cessation of tobacco use and harmful use of alcohol) is a critical component of good hypertension management and is often recommended as a first step for patients with blood pressure of SBP 130—139 mmHg and/or DBP 80—89 mmHg who do not have other CVD risk factors.
- ➢ However, in settings where people do not regularly visit the doctor, people who are recommended *only* lifestyle modification may not return for re-evaluation and needed treatment, resulting in uncontrolled hypertension and associated complications.

Non pharmacologic (Life Style interventions)

- All patients diagnosed to have hypertension should be given lifestyle interventions which include:
    - o Weight loss: goal BMI 18.5-24.9; aerobic exercise: ≥30min exercise/day, ≥5d/week
    - o Consume healthy diet: Diet rich in fruit and vegetables, low in saturated and total fat (DASH)
    - o Avoid salt consumption “table salt”
    - o Engage in physical activity,
    - o Avoid smoking and alcohol

- **For uncomplicated Stage I hypertension life style intervention can be tried for 3 months before initiation of medications. If failed to achieve a blood pressure of less than 140/90 mmHg, then initiation of antihypertensive medication is recommended.**

Pharmacologic (Drug Treatment)

Indications:

- Patient who couldn't achieve target blood pressure with life style interventions.
- At initial presentation in those with:
    - End-organ damage or high WHO cardiovascular risk (>20%)
    - Hypertensive Crises

- **Threshold for treatment**: all patients including diabetes and CKD
    - Age <80 years: ≥140/90mmHg
    - Age >85 years: ≥160/90mmHg
- **Treatment Goal:** all patients including diabetes and CKD
    - Age <80 years: ≤140/90mmHg
    - Age >85 years: ≤160/90mmHg
- **Treatment targets**
    - For most patients, blood pressure is considered controlled when BP is <140/90 mmHg.

Initial monotherapy in uncomplicated hypertension:

CCB (Calcium channel blocker)

- Long-acting dihydropyridine **calcium channel blocker** such as amlodipine as **first line** drug for the treatment of uncomplicated essential hypertension in our country.
- It is probably effective for all races; reduces need for monitoring of electrolytes and renal function; avoids need for different treatment for women of childbearing age who may become pregnant.
    - *Dose: **Amlodipine 5 mg daily**, escalate to 10 mg if BP is uncontrolled.* Usual dosage range: 5 to 10 mg once daily. Target dose: 10 mg once daily.
        - In general, titrate every 7 to 14 days. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

    Or

    - **Nifedipine** (Extended release): Initial: 30 or 60 mg, PO, daily; usual dosage range: 30 to 90 mg daily; maximum: 90 to 120 mg daily

2. **Thiazide diuretics; add on therapy to CCB**

- **Thiazide diuretics** such as hydrochlorothiazide to be used as **add on** when target BP not achieved on long-acting dihydropyridine calcium channel blocker such as amlodipine.
- It is less expensive than other hypertension medications in our setting and are probably effective for all races.
- Because of the lack of evidence with the readily available thiazide diuretics such as hydrochlorothiazide as monotherapy with regards to CVD event reduction, the risk of hypokalemia and the unfavorable effects on lipid and

glucose associated with the drug which necessitates laboratory monitoring, we suggest to be used as add on.

- *Dose:* ***Hydrochlorothiazide;*** Initial: 12.5 to 25 mg, PO, daily; may increase dose to a target dose range of 25 to 50 mg once daily in 1 to 2 divided doses; usual dosage range: 12.5 to 50 mg daily

3. ACE inhibitors; third agent add on therapy

- If a third agent is needed, the alternative class of medication is **ACE inhibitors** considering cost of the drug and availability in Ethiopia.
    - *1st line:* ***Lisinopril,*** **5 mg, PO, daily** (maintained on a diuretic) **or 10 mg, PO, daily** (not maintained on a diuretic)
        - Adjust dose according to blood pressure response. Target dose; 40 mg, PO, daily; usual dosage range: 10 to 40 mg daily
        - **Note:** Antihypertensive effect may diminish toward the end of the dosing interval especially with doses of 10 mg daily. An increased dose may aid in extending the duration of antihypertensive effect. Doses up to 80 mg daily have been used, but do not appear to give greater effect. If possible, consider discontinuing diuretics 2 to 3 days prior to initiating lisinopril; restart diuretic, if needed, after blood pressure is stable.
    - *2nd line;*
        - **Enalapril** Initial: 5 mg, PO, daily (2.5 mg, PO, daily in patients taking diuretics); titrate upward, usually at 1- to 2-week intervals; usual dose range: 10 to 40 mg daily. Target dose: 20 mg daily in 1 or 2 divided doses. Maximum: 40 mg/day.
            - **Note:** May add a diuretic if blood pressure cannot be controlled with enalapril alone.

          Or
        - **Captopril;** Initial dose: 25 mg, PO, BID to TID (a lower initial dose of 12.5 mg, PO, TID may also be considered; may increase at 1- to 2-week intervals up to 50 mg PO TID; maximum dose: 450 mg/day
            - add thiazide diuretic, unless severe renal impairment coexists then consider loop diuretic, before further dosage increases or consider other treatment options

4. ARB (Angiotensin II Receptor Blocker;**)**

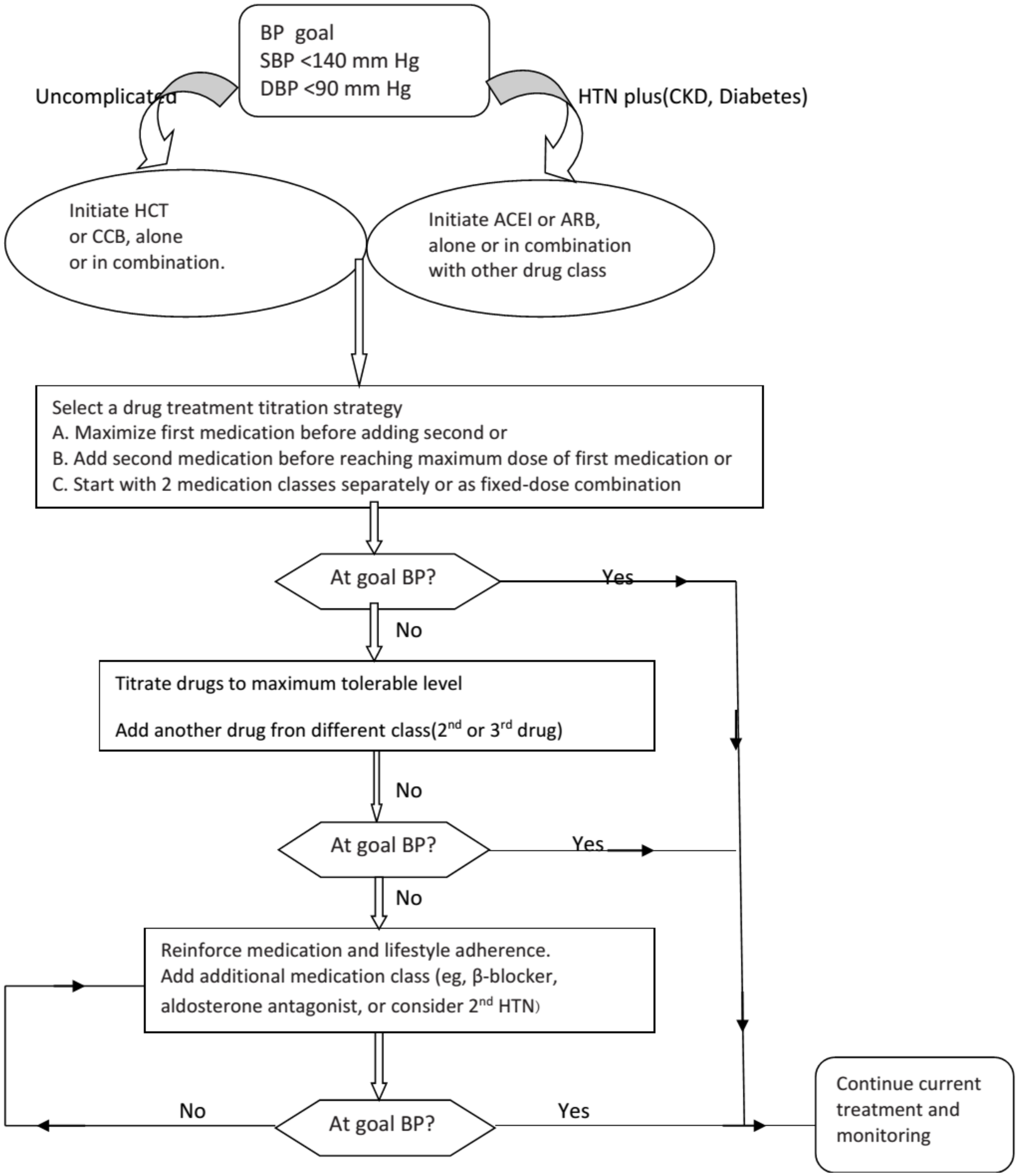
- Antihypertensive effect usually observed within 2 weeks; maximum antihypertensive effect seen within 4 to 6 weeks. Dosage must be individualized. Consider lower initial dosages in volume depleted patients; if possible, correct volume depletion prior to administration.

- **Candesartan;** Initial: 16 mg, PO, daily; titrate to response; usual range: 8 to 32 mg/day in 1 to 2 divided doses; target dose: 12 to 32 mg daily; maximum daily dose: 32 mg daily.

  Or
- **Valsartan;** Initial: 80 mg or 160 mg, PO, daily (in patients who are not volume depleted); dose may be increased to achieve desired effect; usual dosage range : 80 to 320 mg, PO, daily; target dose: 160 to 320 mg, PO, daily; maximum dose: 320 mg/day.

Pharmacologic option in Uncomplicated HTN: no end organ damage

First line ✓ Hydrochlorothiazide 25mg/day ✓ Nifedipine (immediate release) 20-40mg/2-3 times /day ✓ Amlodipine/felodipine 2.5-10 mg once daily (escalate 2.5mg every week)
2nd line ✓ Enalapril 2.5-40 mg in 2 divided doses ✓ Captopril 12.5-100mg TID ✓ Lisinopril 10-40 mg/day ✓ Candesartan 8-32 mg/day in 1-2 divided doses
Alternative second lines ✓ Beta blockers: selective β/α or non-selective e.g. Metoprolol, atenolol, propranolol, carvedilol ✓ Central acting: methyldopa, clonidine


BP goal
SBP <140 mm Hg
DBP <90 mm Hg
Uncomplicated
HTN plus(CKD, Diabetes)
Initiate HCT or CCB, alone or in combination.
Initiate ACEI or ARB, alone or in combination with other drug class
Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination
At goal BP?
Yes
No
Titrate drugs to maximum tolerable level
Add another drug fron different class(2nd or 3rd drug)
No
At goal BP?
Yes
No
Reinforce medication and lifestyle adherence.
Add additional medication class (eg, β-blocker, aldosterone antagonist, or consider 2nd HTN)
No
At goal BP?
Yes
Continue current treatment and monitoring

Resistant hypertension: refers to patients with blood pressures persistently >140/90 mmHg despite taking three or more antihypertensive agents, including a diuretic, in reasonable combination and at full doses

1.5.1 Hypertensive crisis

Definition of Hypertensive urgency and Emergencies and Their Clinical Presentation

- **Hypertensive urgency:** BP ≥ 180/110 mmHg with minimal or no target organ damage
- A **hypertensive emergency** is the association of substantially elevated BP with acute Hypertension Mediated Organ Damage (acute HMOD).
  - ✓ Usually BP ≥ 180/110 mmHg, but there is no specific BP threshold to define a hypertensive emergency.
- Target organs include the retina, brain, heart, large arteries, and the kidneys
  - o Neurologic damage: encephalopathy, stroke/TIA, papilledema(fundoscopy)
  - o Cardiac damage: acute heart failure/pulmonary edema, ACS, aortic dissection
  - o Renal damage: acute renal failure/proteinuria, hematuria, cast
  - o Microangiopathic hemolytic anemia: preeclampsia/Eclampsia
- This situation requires rapid diagnostic workup and immediate BP reduction to avoid progressive organ failure.
- Intravenous therapy is usually required.
- The choice of antihypertensive treatment is predominantly determined by the type of organ damage.

Precipitants:

- Progression of essential hypertension +/- medical noncompliance
- Progression of renovascular disease: AGN, preeclampsia
- Endocrine: pheochromocytoma
- Cerebral injury (low BP in acute stroke- with treatment)

Specific clinical presentations of hypertensive emergencies include:

- **Malignant hypertension:** Severe BP elevation (commonly >200/120 mm Hg) associated with advanced bilateral retinopathy (hemorrhages, cotton wool spots, papilledema).
- **Hypertensive encephalopathy:** Severe BP elevation associated with lethargy, seizures, cortical blindness and coma in the absence of other explanations.
- **Hypertensive thrombotic microangiopathy:** Severe BP elevation associated with hemolysis and thrombocytopenia in the absence of other causes and improvement with BP-lowering therapy.
- Other presentations of hypertensive emergencies include severe BP elevation associated with cerebral hemorrhage, acute stroke, acute coronary syndrome, cardio- genic pulmonary edema, aortic aneurysm/dissection, and severe preeclampsia and eclampsia.

☛ Patients with substantially elevated BP who lack acute HMOD are not considered a hypertensive emergency and can typically be treated with oral antihypertensive therapy

Basic investigations:

- ECG, BUN, Cr, electrolyte, Urinalysis, CXR (optional)

Clinical Presentation and Diagnostic Workup

- The clinical presentation of a hypertensive emergency can vary and is mainly determined by the organ(s) acutely affected.
- There is no specific BP threshold to define a hypertensive emergency.
- Symptoms include headaches, visual disturbances, chest pain, dyspnea, neurologic symptoms, dizziness, and more unspecific presentations.
- Medical history: preexisting hypertension, onset and duration of symptoms, potential causes (nonadherence with prescribed antihypertensive drugs, lifestyle changes, concomitant use of BP elevating drugs [NSAIDS, steroids, immunosuppressants, sympathomimetics, cocaine, antiangiogenic therapy]).

Treatment of hypertensive crisis:

- The type of acute HMOD is the main determinant of the preferred treatment choice.
- The timeline and magnitude of BP reduction is strongly dependent on the clinical context. For example, acute pulmonary edema and aortic dissection require rapid BP reduction, whereas BP levels not exceeding 220/120 mm Hg are generally tolerated in acute ischemic stroke for certain periods.
- **Emergency: decrease MAP by ≈25% in minimum of 2 hours by IV agents; Goal BP ≤ 160/100 mmHg** within 2-6 hours, as tolerated
- **Urgency: decrease BP in hours/days using PO agents**; **Goal normal BP in ≈ 1-2 days**
- Always watch for: UOP, creatinine, mental status; which may indicate lower BP is not tolerated
- **NB:** basically, hypertensive emergency should be treated with IV agents but in shortage of appropriate drugs we can use a hydralazine with short acting PO drugs (captopril, propranolol, nifedipine) for almost all cases of emergency
- **Patients with hypertensive emergencies should be admitted to an ICU**

Drug selection[2]:

- ✓ **Hydralazine**: 10-20mg, IV, q20-30 min for maximum of 3-4 doses; fall in BP begins within 10 to 30 minutes and lasts 2 to 4 hours **combined with one of the following**;
    - **Propranolol 20mg Po stat** and evaluate: (i.e. if no contraindication for propranolol/overt heart failure or severe COPD start with hydralazine)
        - Patients with ACS and aortic dissection (avoid reflex tachycardia)

---

[2] Source; Cardiology handbook, university of Gondar hospital, management guidelines, 2014

    - Acute renal failure/ATN
  - **Captopril 12.5mg PO stat** and evaluate
    - Caution in patients with acute renal failure and better to use propranolol, and also use captopril if the patient is not volume overloaded like Overt heart failure/pulmonary edema
    - Encephalopathy and stroke (ischemic or hemorrhagic if indicated)
  - **Nifedipine 20mg Po stat** and evaluate (use if propranolol and captopril are not available or contraindicated)
    - Acute renal failure
    - Encephalopathy and stroke

NB:

- Caution in combination of hydralazine with nifedipine (reflex tachycardia)
- For acute stroke (ischemic, hemorrhagic, SAH) BP should be kept a bit higher 180-185/100 - 110mmHg until the acute event passed.
- **Sublingual nifedipine is contraindicated**[3] in this setting and should **not** be used. Cerebral or myocardial ischemia or infarction can be induced by aggressive antihypertensive therapy if the blood pressure falls below the range at which tissue perfusion can be maintained by autoregulation. This has been most often described with sublingual nifedipine, which may produce an unpredictable and uncontrolled blood pressure reduction as well as severe ischemic complications

- During our clinical attachment, for Acute hypertension (urgey/emergency): we were using Captopril[4] Oral, sublingual: 12.5 to 25 mg, may repeat as needed; we consider alternative therapy if blood pressure is nonresponsive within 20 to 30 minutes (hydralazine was preferred in preeclampsia with severity features [BP ≥ 160/110] and eclampsia)
  - In this obstetric complication, we were practicing like this;
    - 1 vial of hydralazine = 1ml = 20mg, so dilute 1ml of hydralazine with 3ml of NS or Distilled water and give 1ml of the dilute (i.e. 5mg every 30min)

Hypertensive Emergencies Requiring Immediate BP Lowering

Clinical Presentation	Timeline and Target BP	First Line Treatment	Alternative
Malignant hypertension with or without thrombotic microangiopathy or acute renal failure	Several hours, MAP −20% to −25%	**Labetalol**, 20mg, over 2 minutes initially then 40-80mg, IV, q10min until target is achieved (max total dose; 300mg)	Hydralazine, 10-20mg, IV, q20-30 min until target is achieved for maximum of 3-4 doses

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[3] Reference; UpToDate, © 2018, version 2.0

[4] Reference; UpToDate, © 2018, version 2.0

Hypertensive encephalopathy	Immediate, MAP −20% to −25%	Labetalol	Hydralazine
Acute ischemic stroke and SBP >220 mm Hg or DBP >120 mm Hg	1 h, MAP −15%	Labetalol	Hydralazine
Acute ischemic stroke with indication for thrombolytic therapy and SBP **>185 mm Hg or DBP >110 mm Hg**	1 h, MAP −15%	Labetalol	Hydralazine
Acute hemorrhagic stroke and SBP >180 mm Hg	Immediate, 130<SBP<180 mm Hg	Labetalol	Hydralazine
Acute coronary event	Immediate, SBP <140 mm Hg	Nitroglycerine	
Acute cardiogenic pulmonary edema	Immediate, SBP <140 mm Hg	Nitroglycerine (with loop diuretic)	loop diuretic
Acute aortic disease	Immediate, SBP <120 mm Hg and heart rate <60 bpm	nitroglycerine and metoprolol	Labetalol or metoprolol
Eclampsia and severe preeclampsia/ HELLP	Immediate, SBP <160 mm Hg and DBP <105 mm Hg	Labetalol and magnesium sulphate	**Hydralazine** (5mg, IV, q20-30 min until target is achieved for maximum of 3-4 doses) or short acting **nifedipine** (20mg, po, BID or sublingual, q30min, until target achieved)

Follow-Up

- Patients who experienced a hypertensive emergency are at increased risk of cardiovascular and renal disease.
- Thorough investigation of potential underlying causes and assessment of HMOD is mandatory to avoid recurrent presentations with hypertensive emergencies.
- Regular and frequent follow-up **(monthly)** is recommended until target BP and ideally regression of HMOD has been achieved.

Notes on specific hypertension medications

- **Pregnant women and women of childbearing age** not on effective contraception should *not* be given ACE inhibitors, ARBs, or thiazide/thiazide-like diuretics; **CCBs should be used**.

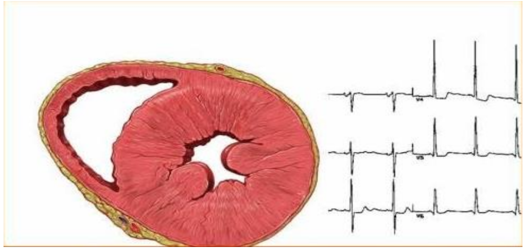
- **Beta blockers are not recommended as first-line therapy**. If a heart attack has been diagnosed within the previous three years, or there is atrial fibrillation or heart failure, then a beta blocker should be added to the starting dose of antihypertensive medication. Patients with angina may also benefit from treatment with a beta blocker.

Common Comorbidities and Complications of Hypertension

- Hypertensive patients have several common and other comorbidities that can affect cardiovascular risk and treatment strategies.
- The number of comorbidities increases with age, with the prevalence of hypertension and other diseases.
- Common comorbidities include coronary artery disease (CAD), Stroke, CKD, HF, DM and COPD.
- Uncommon comorbidities include Rheumatic diseases and psychiatric diseases.
- Lifestyle changes are recommended (smoking cessation, diet and exercise).
- BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80 mm Hg (<140/80 in elderly patients) in patients with comorbidities.

Hypertensive heart disease (HHD)

- Heart disease is the most common cause of death in hypertensive patients
  - LVH, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias
- CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two
- Diastolic dysfunction is an early consequence of hypertension related heart disease



Image; LVH

- ➢Hypertension is a risk factor for the development of HF with reduced ejection fraction (HFrEF), and with preserved ejection fraction (HFpEF).
- ➢Clinical outcome is worse and mortality is increased in hypertensive patients with HF.
- ➢Lifestyle changes are recommended (diet and exercise).
- ➢Treating hypertension has a major impact on reducing the risk of incident HF and HF hospitalization, aggressive control of hypertension can regress or reverse LVH.
- ➢BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80 mm Hg but >120/70 mm Hg.

1.6 Infective endocarditis (IE)

- ❖ IE is defined as an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect.
- ❖ Always suspect endocarditis in a patient with a new heart murmur and unexplained fever or bacteremia.

Risk factors

- ✓ Structural heart disease (esp. Rheumatic regurgitant valve lesions)
- ✓ Prosthetic valves
- ✓ Prior history of IE
- ✓ Injection drug use
- ✓ Recent dental manipulation, GI, GU instrumentation

Classifications

- ❖ Classified into four groups:
  - ✓ Native Valve IE
  - ✓ Prosthetic Valve IE
  - ✓ Intravenous drug abuse (IVDA) IE
  - ✓ Nosocomial IE

Further Classification

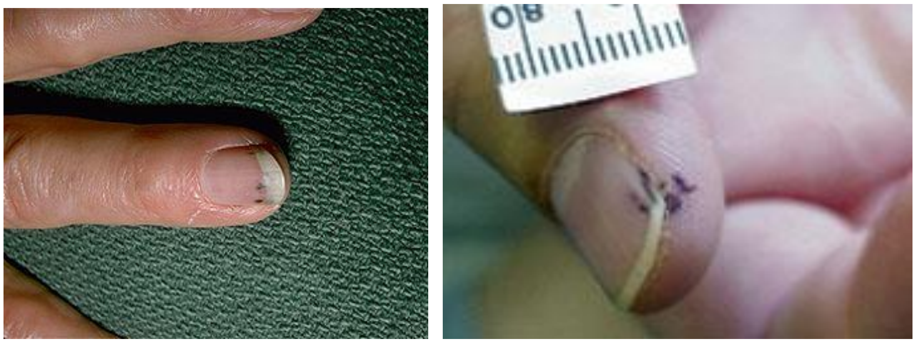
Acute endocarditis	**subacute endocarditis**
✓Most commonly caused by *S. aureus* (highly virulent).	✓Caused by less virulent organisms, such as *S. viridans* and *Enterococcus*
✓Occurs on a normal heart valve.	✓Occurs on damaged heart valves
✓Rapidly destructive, Metastatic foci	✓Indolent nature

✓If untreated, fatal in less than 6 weeks.	✓If untreated, takes much longer than 6 weeks to cause death

Clinical presentations

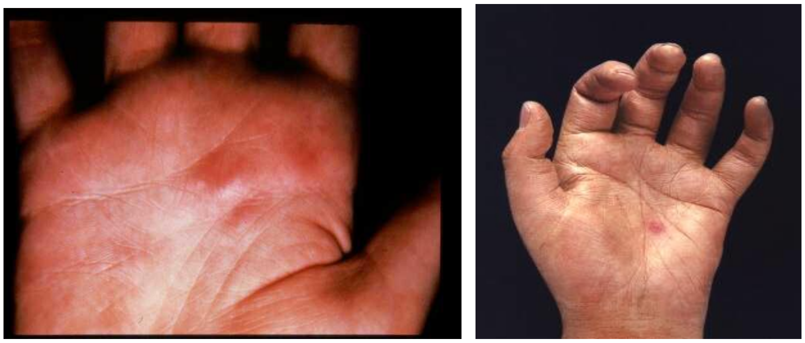
- History
  1. **Acute endocarditis** is characterized by high grade fever with rapidly progressive heart failure and metastatic infection. Common etiologies include S.aureus, pneumococci, and enterococci
  2. **Subacute endocarditis**- evolves during weeks to months with only modest toxicity. It is commonly caused by viridians streptococci, CONS, Enterococci, and HACEK group
- Common findings include
  - ✓ Persistent fever
  - ✓ Heart murmurs
  - ✓ Otherwise-unexplained arterial emboli, and
  - ✓ Cutaneous and mucocutaneous lesions, like petechiae, splinter hemorrhages, janeway lesions, osler's node, and Roth spots.

Splinter Hemorrhages



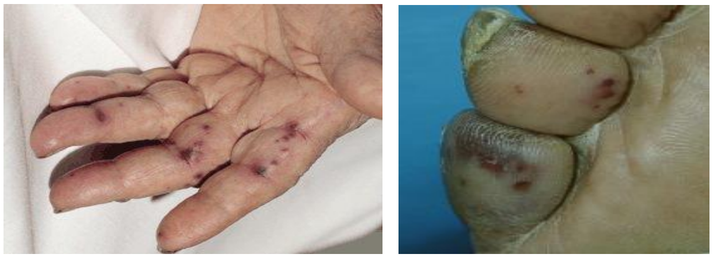
Nonspecific, non-blanching, Linear reddish-brown lesions found under the nail bed, usually do NOT extend the entire length of the nail. Subungual hemorrhages that extend the entire length of the nail or are primarily located at the proximal end of the nail (near the cuticle) are like due to trauma.

Janeway lesions



Erythematous, blanching macules, nonpainful, more specific, located on palms and soles

Osler's Nodes



More specific, painful and erythematous nodules, located on pulp of fingers and toes, more common in subacute IE

Diagnosis

- IE should be suspected in any patient with rheumatic VHD (esp. regurgitant) presenting with fever and/or worsening of heart failure despite therapy.
- Blood culture
  - 3 sets of blood culture should be obtained prior to antibiotic therapy.
  - A minimum of 10ml of blood for each set
  - Each set of cultures should be taken from separate venipuncture sites
  - Avoid taking samples from preexisting IV lines
  - Blood cultures can be taken at any time.
  - Acutely ill pt
    - Take 3 blood culture samples over 1hr before beginning empiric therapy
  - Subacute endocarditis
    - Take 3 samples over 12hrs
- Echocardiography
  - Look for vegetations, abscess, new valvular regurgitation, or new partial dehiscence of prosthetic valve.

- ✓ Trans esophageal echo (TEE) is better than transthoracic echocardiography (TTE) in the diagnosis of endocarditis for especially mitral valve pathology and small aortic vegetations.
- ✓ Most patients should get TTE as an initial screening test.
  - ☛ N.B. echocardiographic evidence of vegetations is not necessary to make the diagnosis as long as sufficient Duke criteria have been met.

- ❖ Diagnosis criteria; use modified Dukes clinical criteria: **2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria** are required to diagnose infective endocarditis.
- ❖ Treatment should be initiated if clinical suspicion is high.

Modified Duke Criteria

Major Criteria

- ➢ Positive blood culture
  - – Typical microorganism for infective endocarditis from two separate blood cultures
  - – Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
    - Blood cultures (≥2) drawn more than 12 hr apart, *or*
    - All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart
  - – Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
- ➢ Evidence of endocardial involvement
  - – Positive echocardiogram
    - Oscillating intracardiac mass, on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomical explanation, *or*
    - Abscess, *or*
    - New partial dehiscence of prosthetic valve, *or*
  - – New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

1. **Predisposing condition** (abnormal valve or abnormal risk of bacteremia like IV drug abuse, GI/GU manipulation….)
2. **Fever ≥38.0°C (100.4°F)**
3. **Vascular phenomena:** Septic arterial or pulmonary emboli, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions[5]

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[5] Janeway lesions are painless erythematous lesions on palms and soles.

4. **Immune phenomena:** Glomerulonephritis, Osler nodes[6], Roth spots[7], rheumatoid factor
5. **Positive blood cultures** not meeting major criteria
6. **Positive echocardiogram** not meeting major criteria

- **Definite IE**
  - **Clinical criteria**
    - 2 major criteria, *or*
    - 1 major and 3 minor criteria, *or*
    - 5 minor criteria
  - Pathologic criteria
    - Microorganism: (via culture or histology) in a valvular vegetation, embolized vegetation, or intracardiac abscess
    - Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
- Possible IE
  - 1 major criterion and 1 minor criterion or
  - 3 minor criteria
- Rejected IE
  - Firm alternative diagnosis for manifestations IE, *or*
  - Sustained resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*
  - No pathological evidence of infective endocarditis at surgery or autopsy

Organisms

- Native valve endocarditis
  - ***S. viridans*** is the most common organism in native valve endocarditis.
  - Other common organisms include:
    - *Staphylococcus* species (***S. aureus*** more commonly than *S. epidermidis*) and *Enterococci.*
    - *Streptococcus bovis* is associated with increased risk of active colonic malignancy
    - **HACEK** group of organisms: *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella.*

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[6] Osler nodes are painful, raised lesions of fingers, toes, or feet.

3 Roth spots are oval, retinal hemorrhages with a clear, pale center.

- Prosthetic valve endocarditis
    - Staphylococci are the most common causes of early-onset endocarditis; symptoms appear **within 60 days of surgery** (*S. epidermidis* more commonly than *S. aureus*).
    - **Streptococci** are the most common cause of **late-onset endocarditis**; symptoms appear 60 days after surgery.
- Endocarditis in IV drug users
    - Frequently presents with **right-sided** endocarditis.
    - ***S. aureus*** is the most common cause.
    - Other organisms include *Enterococci* and *Streptococci.*
    - Fungi (mostly *Candida*) and gram-negative rods (mostly *Pseudomonas*) are less common causes.

Treatment of IE

❖ PRINCIPLES OF TREATMENT

1) **Parentral** antibiotics
2) Only **bactericidal** antibiotics are effective and Bacteriologic result should direct antibiotic selection
3) **High dose & combination** of antibiotics designed to give sustained bactericidal serum concentration to penetrate vegetations!
4) **Prolonged treatment** to kill dormant bacteria clustered in vegetations! (4-6 wks)
5) **3 sets of blood cultures should be drawn prior to initiating antibiotic therapy.** start antibiotic treatment immediately after blood culture is collected over 1 hour in Acute endocarditis or prosthetic valve endocarditis.

- Subacute endocarditis (SBE)- if patient hemodynamically stable wait for 2-3 days till blood culture result is collected

    - ✓ Culture positive
        - Treat based on the isolated organism and susceptibility pattern
    - ✓ Culture negative endocarditis
        - **SBE- ceftriaxone 2gm/day + gentamycin 3mg/kg** for the first 2wks and continue with ceftriaxone only for the remaining wks of therapy
        - **Acute endocarditis**- continue **vancomycin + gentamycin** for 2 wks and then vancomycin only for the remaining wks of therapy
            - Patients with proven or suspected enterococcal endocarditis should receive combination of vancomycin and gentamicin for the whole duration of therapy
            - If vancomycin is not available or patient cannot afford, use ceftriaxone 2gm/day with gentamycin
            - **In our setup we are using ceftriaxone and gentamycin**

as 1st line because of availability and cost effectiveness but not efficacy.

- Duration of therapy- Parenteral antibiotics based on culture results for extended periods (4 weeks for most patients, sometimes for 6 weeks)
    - ✓ Indications for 6 weeks of antibiotic therapy
        - Patients with slow clinical response than expected
        - Presence of cardiac or extracardiac complications
        - Patients with infections of long duration prior to diagnosis
        - Infection with highly virulent or resistant organisms
- If cultures are negative but there is high clinical suspicion, treat empirically (See table below) until the organism can be isolated.
- Anticoagulants and antiplatelets are not recommended to prevent or treat embolic complications.

Monitoring during therapy

- ❖ T^0 should be followed at least 4 times a day.
    - ✓ Fever should subside after 5-7 days of antibiotics.
    - ✓ If fever persists beyond 7 days despite appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess, extracardiac abscess (spleen, kidney), or complications (embolic events), resistant organisms like enterococci
- ❖ Repeating blood culture can be considered in those patients with initial positive cultures and
    - ✓ Suboptimal clinical response after 1 week of antibiotic therapy
    - ✓ After completing the course of antibiotic therapy
- ❖ CBC, ESR and RFT should be done at least every week to check for drug toxicities and response

- If patient has intracardiac devices such as pacemaker or ICD, these must be *removed.*
- Early surgical intervention is warranted for patient with:
    - ○ Acute heart failure due to valvular damage.
    - ○ Left-sided IE with highly resistant organisms (including MRSA)
    - ○ IE complicated by heart block or intracardiac abscess.
    - ○ Persistent bacteremia or fevers lasting 5 to 7 days after antibiotic initiation.
    - ○ Recurrent infection in those with prosthetic valves.

Note: Infective endocarditis is almost always fatal if left untreated.

Empiric antibiotic therapy

Table: Empiric treatment of **“community acquired” Native Valve SBE**

Antibiotic regimen options	**Dosage and route**	**Duration (weeks)**	**Comments**
Ceftriaxone PLUS **Gentamicin**	2g, IV, once per day	4-6	If vancomycin is not available or patient cannot afford
	3mg/kg, IV, daily OR 1mg/kg/dose, IV, TID	2	Dose should be adjusted to Creatinine clearance. Creatinine should be monitored.
Vancomycin PLUS **Gentamicin**	15mg/kg/dose, IV, BID	4	For patients with severe or immediate **beta-lactam allergy.** Do not exceed 2g per day Adjust dose to creatinine clearance.
	3mg/kg, IV, daily OR 1mg/kg/dose, IV, TID	2	See above

*Treatment should be modified based on culture and sensitivity results as well as clinical judgement of response, risk factors and expected organisms.

Table: Empiric treatment of **health care - associated and IV medicine users endocarditis**

Vancomycin PLUS	15mg/kg/dose, IV, BID	4	-Do not exceed 2g per day -Adjust dose to creatinine clearance.
Gentamicin	3mg/kg, IV, daily OR 1mg/kg/dose, IV, TID	2	See the table above

Prophylaxis

- Scope of patients who qualify for prophylaxis is much narrower than in the past.
- Must have both a qualifying cardiac indication **AND** procedure to warrant antibiotic prophylaxis.
- Qualifying cardiac indications
    - ✓ Prosthetic heart valves (including mechanical, bioprosthetic, and transcatheter valves).
    - ✓ History of infective endocarditis
    - ✓ Congenital heart disease
        - Unrepaired cyanotic congenital heart disease.
        - Repaired congenital heart disease, with prosthetic material, during first 6 months after procedure
    - ✓ Cardiac transplant with valvopathy.
- Qualifying procedures
    - ✓ Dental procedures involving manipulation of gingival mucosa or periapical region of teeth (extractions, implants, periodontal surgery, cleaning when bleeding expected).
    - ✓ Procedures involving biopsy or incision of respiratory mucosa
    - ✓ Procedures involving infected skin or musculoskeletal tissue

Indications for surgery in IE

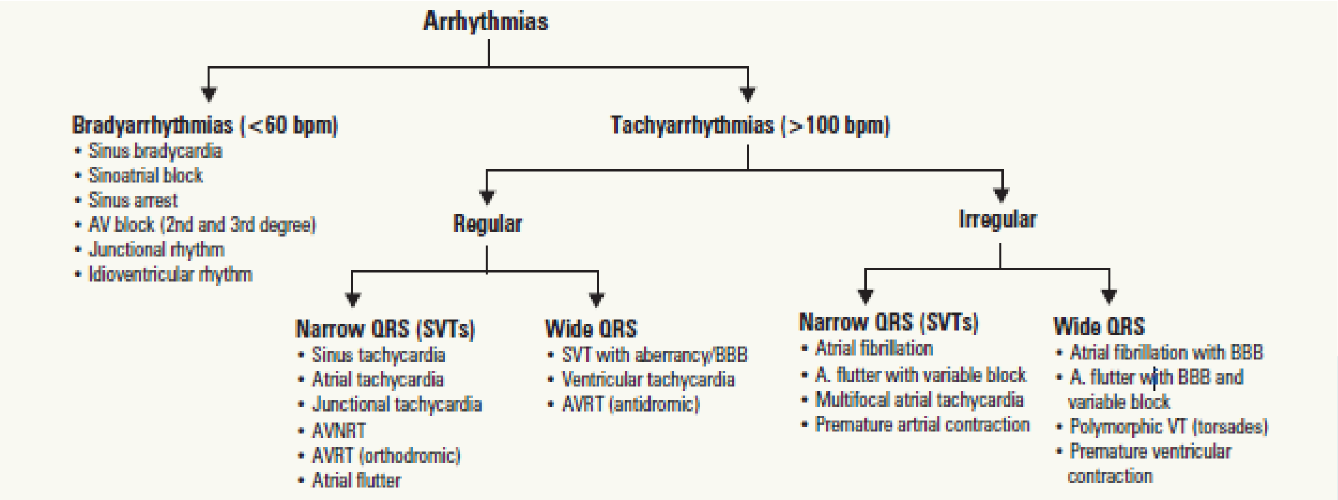
- Significant embolic events
- Persistent infection, and
- Progressive cardiac failure

1.7 Arrhythmia

Readers are recommended to click here and read → Chapter 6; Basics of ECG and ECG interpretation before reading arrythmia.

- Arrhythmias are disorders of cardiac rate, rhythm and conduction.
- Arrhythmias are classified as bradyarrhythmia's and tachyarrhythmias
- Bradyarrhythmia's include sinus bradycardia, sinus pauses and atrioventricular blocks.
- The tachyarrhythmias can further be classified into supraventricular and ventricular arrhythmias, based on their site of origin.

  - Supraventricular tachyarrhythmias includes atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia and multifocal atrial tachycardia.
  - Ventricular tachyarrhythmias include ventricular tachycardia and ventricular fibrillation.
- The etiologies for arrhythmias are:
  - Structural heart disease (VHD, CMP, CAD)
  - Thyrotoxicosis
  - Electrolyte abnormalities
  - Ingestion of stimulants
  - Side effects of some medicines (digoxin, antiarrhythmic medicines)
- Clinical features of arrythmias in general include:
  - Palpitation
  - Shortness of breath
  - Dizziness/syncope
  - Sensation of a pause in the heart beat
  - Chest discomfort that mimics symptoms of myocardial ischemia(angina)
  - Development of Heart Failure or decompensation of previously existing Heart Failure
  - Sudden death
- ECG is the main stay of diagnosis.
  - Other investigations like Echo, CXR, TFT, CBC, electrolytes should be guided by clinical data.
  - Prior to treatment of any suspected arrhythmia the diagnosis should be confirmed with ECG.
    - ☛ It is dangerous to give any antiarrhythmic medicine without doing ECG!


Arrhythmias
Bradyarrhythmias (<60 bpm)
• Sinus bradycardia
• Sinoatrial block
• Sinus arrest
• AV block (2nd and 3rd degree)
• Junctional rhythm
• Idioventricular rhythm
Tachyarrhythmias (>100 bpm)
Regular
Irregular
Narrow QRS (SVTs)
• Sinus tachycardia
• Atrial tachycardia
• Junctional tachycardia
• AVNRT
• AVRT (orthodromic)
• Atrial flutter
Wide QRS
• SVT with aberrancy/BBB
• Ventricular tachycardia
• AVRT (antidromic)
Narrow QRS (SVTs)
• Atrial fibrillation
• A. flutter with variable block
• Multifocal atrial tachycardia
• Premature artrial contraction
Wide QRS
• Atrial fibrillation with BBB
• A. flutter with BBB and variable block
• Polymorphic VT (torsades)
• Premature ventricular contraction

SVT = Supraventricular tachycardia, PVCs = premature ventricular contractions, AVNRT = Atrioventricular node reentry tachycardia, AVRT = Atrioventricular reentrant tachycardia.

Figure; Clinical approach to arrhythmias

1. Tachyarrhythmias

1.1 Supraventricular tachyarrhythmias

1.1.1 Paroxysmal supraventricular tachycardia

- ❖ Paroxysmal supra-ventricular tachycardia (PSVT) is an intermittent narrow complex tachyarrhythmia other than Atrial Fibrillation, atrial flutter, and MAT (Multifocal Atrial Tachycardia).
- ❖ PSVT usually occurs in individuals without underlying structural heart disease.
- ❖ ECG shows regular narrow QRS tachycardia. P wave may be seen preceding or following or superimposed on QRS complex or may not be seen.

Treatment

Non pharmacologic

- ❖ **Vagal maneuvers**: maneuvers which increase vagal activity can terminate episodes of PSVT. ECG and blood pressure monitoring is required during the procedure.
    - ☛ ***Carotid sinus massage***: supine position with the neck extended. The carotid sinus is located inferior to the angle of the jaw at the level of the thyroid cartilage. Steady pressure is applied to one carotid sinus for 5 to 10 seconds. If no response, repeat it in the contralateral side after 1-2 minutes.

    Note: Carotid massage should not be attempted in patients with carotid bruit/stenosis or ischemic stroke. Both carotid sinuses should never be massaged simultaneously.

    - ☛ ***Valsalva maneuver***: while in the supine position the patient is instructed to exhale forcefully against a closed glottis with closed mouth and nose for 10 seconds. Adequacy indicated by neck vein distension, and increased tone in the abdominal wall muscles.
- ❖ **Synchronized electrical Cardioversion**: required rarely for hemodynamically unstable patients. The energy needed is 150 to 200 joules for monophasic defibrillators.

Pharmacologic

Termination of acute episode
First line

- ✓ Adenosine, I.V, very rapidly (over 1-2 seconds): Initial: 6mg; if not effective within 1-2 minutes, 12mg may be given; may repeat 12mg bolus if needed. Follow each dose with 20ml very rapid NS flush.

Alternatives

- ✓ Metoprolol, IV, 2.5-5mg every 2-5 minutes (maximum total dose: 15mg over a 10-15minute period). ***OR***
- ✓ Verapamil, I.V, 2.5-5mg over 2 minutes; second dose of 5-10mg may be given after 15-30 minutes; maximum total dose: 20-30mg **OR**
- ✓ Digoxin, 0.5 to 1mg IV over a period of 10 to 15 min followed by 0.25mg every 2-4 hours with a total dose less than 1.5mg with in 24-hour period

Prevention of recurrence (chronic therapy)

First line: beta blockers

- ✓ Metoprolol succinate (Extended release): 25-200mg/day, P.O. **OR**
- ✓ Atenolol, 25-100mg/day, P.O. **OR**
- ✓ Propranolol 10-40mg P.O. 3-4 times daily

Alternatives

- ✓ Verapamil, immediate release 40-120mg, P.O.TID or extended release 180-360mg/day

1.1.2 Atrial fibrillation and flutter

Atrial fibrillation

- **Atrial fibrillation** is marked by disorganized, rapid, and irregular atrial activation which results in irregular ventricular response.
- The ventricular rate is usually rapid.
- The ECG in Atrial Fibrillation is characterized by the lack of P-waves, irregularly irregular ventricular response and narrow QRS.

Atrial flutter

- **Atrial flutter** is characterized by regular rapid atrial rate of **260 - 300 beats** per minute, which usually results in a regular ventricular response in a 2:1 ratio resulting in a heart rate of 130 - 150 beats per minute.
- The ventricular response can sometimes be in 3:1, 4:1, irregular or rarely 1:1 ratio.
- **The typical ECG finding is of saw-tooth appearance of the baseline mainly on inferior leads (II, III, AVF) with rapid, regular and narrow QRS**.

Treatment

Note: The management of atrial fibrillation and atrial flutter are the same.

Non pharmacologic

- ❖ Avoid stimulants (e.g. Caffeine, Khat) and alcohol intake.

- ❖ Immediate electrical cardio-version-associated with hemodynamic instability (cardiogenic shock) due to a rapid ventricular rate.
- ❖ If hypotension occurs at ventricular rate <130 beats/min, other causes of hypotension should be investigated.
- ❖ The energy requirement is usually 100 to 200 joules; it should be synchronized.

Pharmacologic

1. **ventricular rate control**

Acute ventricular rate control

First line

- ✓ Metoprolol, 2.5 - 5mg, IV, over 3—5 min, to maximum total dose 15mg over 10-15 minutes

Alternative

- ✓ Digoxin, 0.25mg, IV, q2h until 1 mg total (digoxin is the first line medicine if atrial fibrillation is associated with severe left Ventricular dysfunction)

Chronic ventricular rate control (Maintenance)

First line: Beta blockers

- ✓ Metoprolol, preferred beta blocker in patients with Heart Failure with depressed LV (left ventricle) systolic function. **OR**
    - ☛ Immediate release (Metoprolol tartrate): 25-100 mg twice daily
    - ☛ Extended release (Metoprolol succinate): 50 - 400 mg/day
- ✓ Atenolol, 25-100mg P.O., daily

Alternatives

- ✓ Digoxin, 0.125 - 0.25mg P.O., daily. **OR**
    - ☛ Digoxin can be added to beta blocker when the ventricular rate control is suboptimal.
    - ☛ It is the preferred agent when Heart Failure due to LV systolic dysfunction is not well controlled.
- ✓ Verapamil, 40-80mg P.O., 2-3 times daily.

2. **Anticoagulation to prevent cardioembolic cerebrovascular accident (CVA)**

- ❖ Risk stratify patients for thrombotic complications with the **CHA$_2$DS$_2$-VASc score.**
- ❖ This is a scoring calculator used to estimate annual stroke risk in a patient with AFib or atrial flutter.

Scoring systems for assessing the risk of stroke (CHA$_2$DS$_2$-VASc) and bleeding (HAS-BLED) in patients with atrial fibrillation

CHA$_2$DS$_2$-VASc	Score	HAS-BLED*	Score
CHF	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function (1 point each)	1 or 2
Age ≥ 75 years old	2	Stroke	1
DM	1	Bleeding tendency/predisposition	1
Stroke/TIA/Thromboembolism	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (e.g. age >65 years old)	1
Age 65 - 74 years old	1	Drugs or alcohol (1 point each)	1 or 2
Sex category (i.e. female sex)	1		
Maximum score	9	Maximum score	9

* The **HAS-BLED bleeding risk** score has only been validated in patients with atrial fibrillation

- ❖ **Hypertension** is defined as SBP >160 mmHg.
- ❖ **Abnormal renal function** is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 2.2 mg/dl or ≥ 200 µmol/L.
- ❖ **Abnormal liver function** is defined as CLD (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2 X the upper limit of normal, plus one or more of ALT, AST, and/or ALP > 3 X the upper limit normal).
- ❖ **Bleeding predisposition** includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion.
- ❖ **Labile INRs** for a patient on warfarin includes unstable INRs, excessively high INRs, or <60 % time in therapeutic range.

CHA$_2$DS$_2$VASc score Interpretation

- ❖ The higher the score, the higher the annual stroke risk.
- ❖ For patients with CHA$_2$DS$_2$VASc score >1, anticoagulation is generally indicated unless high bleeding risk
  - ○ **Score 0 → No antithrombotic**
  - ○ **Score 1 → Anti-platelet or anticoagulation**
  - ○ **Score ≥ 2 → anticoagulation.**
- ❖ Commonly used Antiplatelets include Aspirin (1st line) & clopidogrel (2nd line). Commonly used anticoagulants include warfarin, UFH, LMWH

HAS-BLED Score Interpretation

0 points:	1.13 bleeds per 100 patient-years
1 point:	1.02 bleeds per 100 patient-years
2 points:	1.88 bleeds per 100 patient-years
3 points:	3.74 bleeds per 100 patient-years
4 points:	8.70 bleeds per 100 patient-years
5 to 9 points:	Insufficient data

Choice of anticoagulant: depends on etiology of AFib or atrial flutter.

- For patients with **mechanical valves, mitral valvular disease, or ventricular assist devices, warfarin is the only oral anticoagulant available**. For other patients, direct oral anticoagulants (DOACs) can be used.
- DOACs approved for AFib include factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) and direct thrombin inhibitors (dabigatran). These agents do not require lab monitoring. Cost is the limiting factor for wider use in resource limited settings like Ethiopia.
- **Rivaroxaban is the available direct oral anticoagulant in Ethiopia.**
  - The dose is Rivaroxaban 20 mg Po daily.
  - Dose adjustment is required for patients with renal failure, elderly, low body weight and those with high risk of bleeding.

Warfarin:

- ✓ Widely available and affordable anticoagulant
- ✓ Warfarin has a narrow therapeutic range and during therapy monitoring using INR is mandatory.
- ✓ An **INR of 2 to 3** is the anticoagulation goal range (**therapeutic range)** for warfarin.
- ✓ Warfarin, starting dose, **2.5 - 5mg/day**, dose **titrated to achieve INR of 2.0-3.0**.
- ✓ The goal is to maintain time in therapeutic (TTR) range above 70 %.

Warfarin dosing and monitoring

Suggested dose changes for maintaining INR within a target range of 2—3

INR	Dose change
<1.5	Increase by 20%
1.6—1.9	Increase by 10%

2-3	Therapeutic range
3.1—3.4	Decrease by 10%, adjustment may not be necessary
3.5—3.9	Decrease by 20%, consider holding one dose
4.0—4.9	Hold dose until INR returns to range then decrease by 20—30%

Management of supratherapeutic INR values

INR	Patient situation	Action
3.1—5.0	No bleeding or need for rapid reversal (i.e., no need for surgery)	Omit next few warfarin doses and/or restart at lower dose when INR approaches desired range. If INR is only minimally above range, no dose reduction may be needed.
5.1—9.0	No bleeding or need for rapid reversal	Omit next 1—2 doses, monitor INR more frequently, and restart at lower dose when INR approaches target range or omit dose and give 1 - 2.5 mg vitamin K orally (use this if patient has risk factor for bleeding).
	No bleeding but reversal needed for surgery or dental extraction within 24 hours	Vitamin K_1 2—4 mg orally (expected reversal within 24 hours); give additional 1—2 mg if INR remains high at 24 hours.
9.1—20.0	No bleeding	Stop warfarin; give vitamin K_1 3—5 mg orally; follow INR closely; repeat vitamin K_1 if needed. Reassess need and dose of warfarin when INR approaches desirable range.
Rapid reversal required (>20.0)	Serious bleeding or major warfarin overdose	Stop warfarin; give vitamin K_1 10 mg by slow IV infusion. May repeat vitamin K_1 every 12 hours and give fresh plasma transfusion or prothrombin complex concentrate as needed. When appropriate, heparin can be given until the patient becomes responsive to warfarin.
Life Threatening Bleeding		Replace with prothrombin complex concentrate and give 10 mg of vitamin K_1 by infusion. May repeat if needed. Give fresh frozen plasma if prothrombin complex concentrates not available.

1.2 Ventricular tachycardia

- Ventricular tachycardias are wide QRS tachyarrhythmias that originate in the myocardium.
- They are commonly associated with some form of structural heart disease.

- Based on their clinical significance, they can be divided in to two:
    1) **Malignant** (potentially lethal) arrhythmias → sustained ventricular tachycardia (VT) and Ventricular fibrillation.
    2) **Non sustained** (hemodynamically tolerated) arrhythmias → premature ventricular contractions (PVCs), non-sustained ventricular tachycardia (NSVT), and accelerated idioventricular rhythm (AIVR).
- Ventricular tachycardia which stays for more than 30 seconds is labeled sustained.
- All Wide QRS (> 120 ms) tachycardias are considered and treated as ventricular tachyarrhythmias until proved otherwise.

Treatment

Non pharmacologic

- CPR should be provided to patients with sustained VT with cardiac arrest (the victim is unresponsive, pulseless and not breathing).
- O_2 via face mask or nasal catheter.
- Continuous ECG monitor.
- Suction device and endotracheal intubation set should be ready.
- Correct electrolyte disorders.
- Reassure patients with non-sustained ventricular tachycardia.

Defibrillation:

- Sustained polymorphic VT, ventricular flutter, or ventricular fibrillation Emergency defibrillation (without synchronization), with >200 Joules (monophasic), increase the energy to the maximum if arrhythmia persists.
- Sustained monomorphic VT: synchronized with >200 Joules (monophasic).

Note:

- *If the hemodynamic status allows conscious sedation should be provided.*
- *DC cardioversion is first line therapy for sustained wide QRS tachycardias.*
- *Pharmacologic treatment may be an acceptable option in hemodynamically stable monomorphic VT with no Heart Failure.*

Pharmacologic
First line:

- ✓ **Amiodarone, IV**
- Stable VT regimen:
    - Step 1: 150mg over first 10 minutes (dilute in 100ml D5W)
    - Step 2: 360mg over next 6 hours (dilute in 500ml D5W): 1 mg/minute
    - Step 3: 540mg (dilute in 500 to 1000ml D5W) over next 18 hours: 0.5mg/minute

- Pulseless VT (cardiac arrest) regimen:
    - ☛ If unresponsive to defibrillation attempts and CPR; Amiodarone, I.V push, 300mg (undiluted)
    - ☛ If VT or VF recurs, administer supplemental dose of 150mg and continue CPR.

Alternative:

- ✓ **lidocaine, IV**
- Both stable VT and Pulseless VT (cardiac arrest) regimen:
    - ☛ Lidocaine, I.V, 1 - 1.5mg/kg; repeat with 0.5 - 0.75mg/kg every 5-10 minutes if no response. (maximum cumulative dose: 3mg/kg).
    - ☛ Follow with continuous infusion of 1 - 4mg/minute
    - ☛ Preparation for continuous infusion: 2g of lidocaine/250ml D5W
    - ☛ Rate of infusion: 1mg/min = 7.5ml/hour, 2mg/min =15ml/hour, 3mg/min= 22.5ml/hr, 4mg/min= 30ml/min

Prevention of recurrence

Non-pharmacologic

- Standard treatment of the underlying cause is the main stay of treatment for preventing recurrent VT. (e.g. treatment of acute coronary syndrome)
- Correct precipitating causes (e.g. hypoxia, hypo/hyperkalemia, acidosis, pulmonary embolism).
- Discontinue arrhythmogenic medicines-digoxin, antiarrhythmic medicines.

Pharmacologic

First line

- ✓ Amiodarone, 400-800mg, PO, BID, for 1-3 weeks
    - ▪ when adequate arrhythmia control is achieved, decrease to 300-400mg, PO, BID to daily for 1 month. Maintenance: 400mg/day

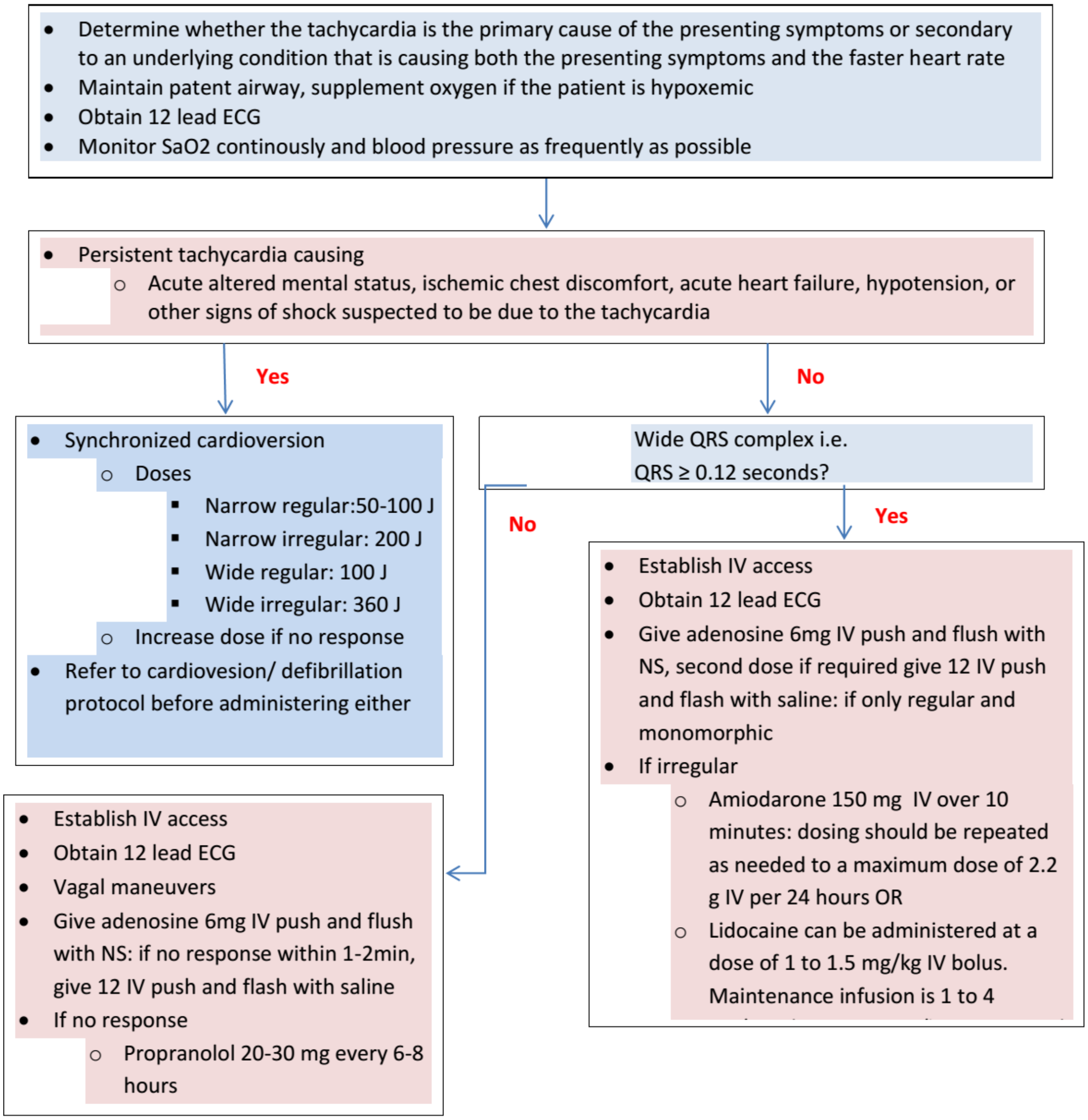
Alternative or additional to Amiodarone → Beta blockers:

- ✓ Metoprolol succinate, extended release: P.O., 25-200mg/day or
- ✓ Atenolol, 25-100mg daily

1.3 Adult tachycardia

Adult Tachycardia

- Heart rate typically of ≥150 beats per minute unless the patient has impaired ventricular function



- Determine whether the tachycardia is the primary cause of the presenting symptoms or secondary to an underlying condition that is causing both the presenting symptoms and the faster heart rate
- Maintain patent airway, supplement oxygen if the patient is hypoxemic
- Obtain 12 lead ECG
- Monitor SaO2 continously and blood pressure as frequently as possible

- Persistent tachycardia causing
  - Acute altered mental status, ischemic chest discomfort, acute heart failure, hypotension, or other signs of shock suspected to be due to the tachycardia

Yes

- Synchronized cardioversion
  - Doses
    - Narrow regular:50-100 J
    - Narrow irregular: 200 J
    - Wide regular: 100 J
    - Wide irregular: 360 J
  - Increase dose if no response
- Refer to cardiovesion/ defibrillation protocol before administering either

No

Wide QRS complex i.e.
QRS ≥ 0.12 seconds?

No

- Establish IV access
- Obtain 12 lead ECG
- Vagal maneuvers
- Give adenosine 6mg IV push and flush with NS: if no response within 1-2min, give 12 IV push and flash with saline
- If no response
  - Propranolol 20-30 mg every 6-8 hours

Yes

- Establish IV access
- Obtain 12 lead ECG
- Give adenosine 6mg IV push and flush with NS, second dose if required give 12 IV push and flash with saline: if only regular and monomorphic
- If irregular
  - Amiodarone 150 mg IV over 10 minutes: dosing should be repeated as needed to a maximum dose of 2.2 g IV per 24 hours OR
  - Lidocaine can be administered at a dose of 1 to 1.5 mg/kg IV bolus. Maintenance infusion is 1 to 4

2. Bradycardia (Bradyarrhythmia)

- AV block describes a delay/block of atrial impulses at the atrioventricular node of varying severity.
- When severe it results in symptomatic bradycardia which can manifest as easy fatigability, Heart Failure, syncope, seizures and bradycardia associated ventricular tachycardias.

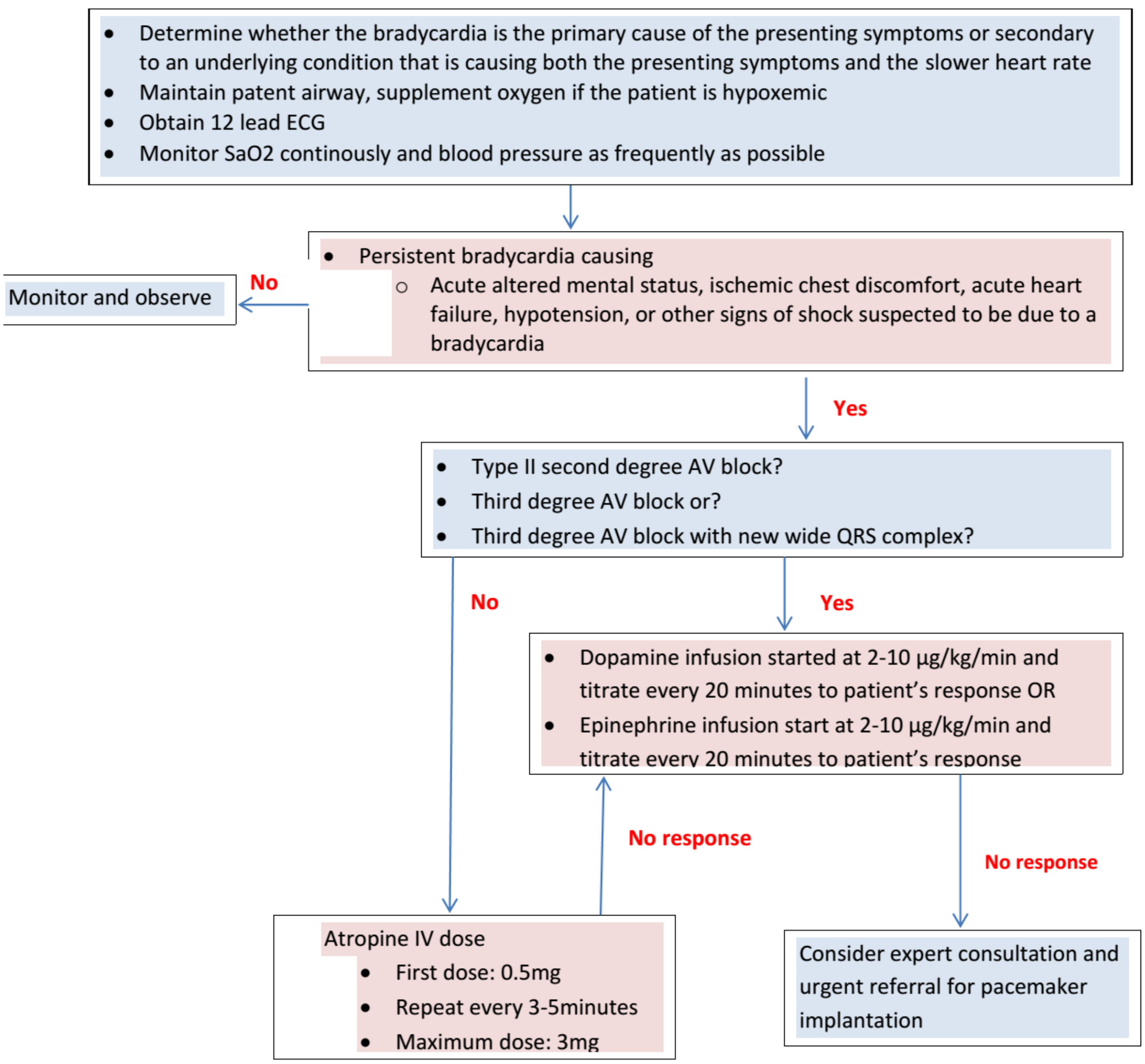
- It is caused by structural heart diseases (mainly IHD, CMP's, CHD), medicines (beta blockers, verapamil, digoxin), electrolyte abnormalities, hypothyroidism and cardiac surgery.
  - ☛ ECG is the diagnostic Ix modality of AV block.

Treatment

- ❖ Look for reversible causes and act accordingly

Adult Bradycardia

Bradycardia: heart rate of <50 beats per minute



- Determine whether the bradycardia is the primary cause of the presenting symptoms or secondary to an underlying condition that is causing both the presenting symptoms and the slower heart rate
- Maintain patent airway, supplement oxygen if the patient is hypoxemic
- Obtain 12 lead ECG
- Monitor SaO2 continously and blood pressure as frequently as possible

- Persistent bradycardia causing
  - Acute altered mental status, ischemic chest discomfort, acute heart failure, hypotension, or other signs of shock suspected to be due to a bradycardia

Monitor and observe

- Type II second degree AV block?
- Third degree AV block or?
- Third degree AV block with new wide QRS complex?

- Dopamine infusion started at 2-10 µg/kg/min and titrate every 20 minutes to patient's response OR
- Epinephrine infusion start at 2-10 µg/kg/min and titrate every 20 minutes to patient's response

Atropine IV dose
- First dose: 0.5mg
- Repeat every 3-5minutes
- Maximum dose: 3mg

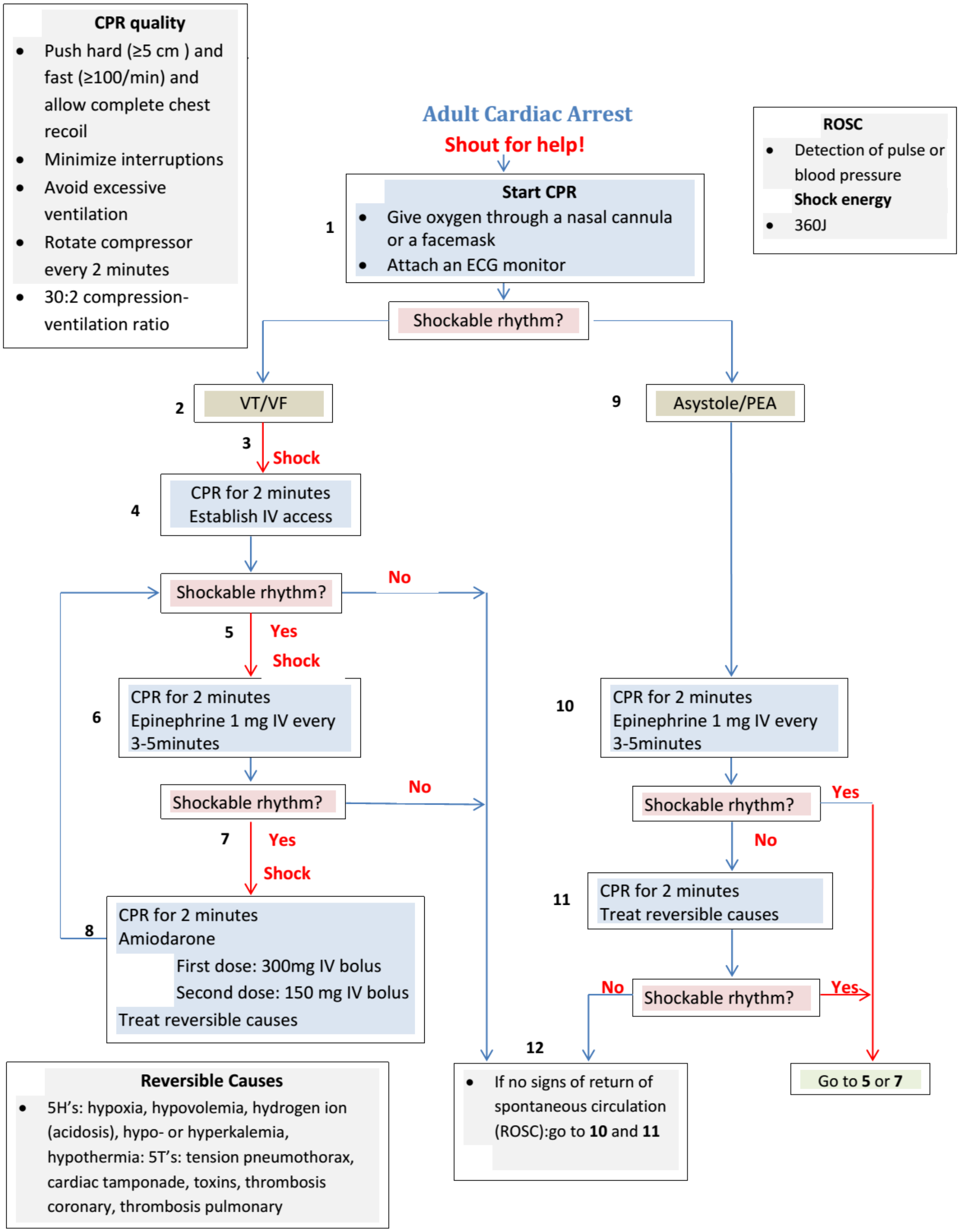
Consider expert consultation and urgent referral for pacemaker implantation

Cardiac arrest (የልብ ምት መቋረጥ)

- [Sudden] cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation.
- If corrective measures are not taken rapidly, this condition progresses to sudden death.
- Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing.
- Sudden cardiac death (SCD) should not be used to describe events that are not fatal."
- These events mostly occur in patients with structural heart disease (that may not have been previously diagnosed), particularly coronary heart disease or sustained ventricular tachycardia/ventricular fibrillation.

Management of cardiac arrest

- Look at the algorism below



CPR quality

- Push hard (≥5 cm) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- 30:2 compression-ventilation ratio

Adult Cardiac Arrest

Shout for help!

ROSC

- Detection of pulse or blood pressure

Shock energy

- 360J

Start CPR

- Give oxygen through a nasal cannula or a facemask
- Attach an ECG monitor

CPR for 2 minutes
Establish IV access

CPR for 2 minutes
Epinephrine 1 mg IV every 3-5minutes

CPR for 2 minutes
Amiodarone
First dose: 300mg IV bolus
Second dose: 150 mg IV bolus
Treat reversible causes

CPR for 2 minutes
Epinephrine 1 mg IV every 3-5minutes

CPR for 2 minutes
Treat reversible causes

- If no signs of return of spontaneous circulation (ROSC):go to **10** and **11**

Reversible Causes

- 5H's: hypoxia, hypovolemia, hydrogen ion (acidosis), hypo- or hyperkalemia, hypothermia: 5T's: tension pneumothorax, cardiac tamponade, toxins, thrombosis coronary, thrombosis pulmonary

- **Sodium bicarbonate** May be considered in the setting of prolonged cardiac arrest only after adequate alveolar ventilation has been established and effective cardiac compressions.

  - Dose: Initial: 1 mEq/kg/dose, IV; repeat doses should be guided by arterial blood gases
  - **Routine use of $NaHCO_3$ is not recommended.**
  - **Note:** In some cardiac arrest situations (e.g. metabolic acidosis, hyperkalemia, or tricyclic antidepressant overdose), sodium bicarbonate may be beneficial.

- Cardioversion and defibrillation

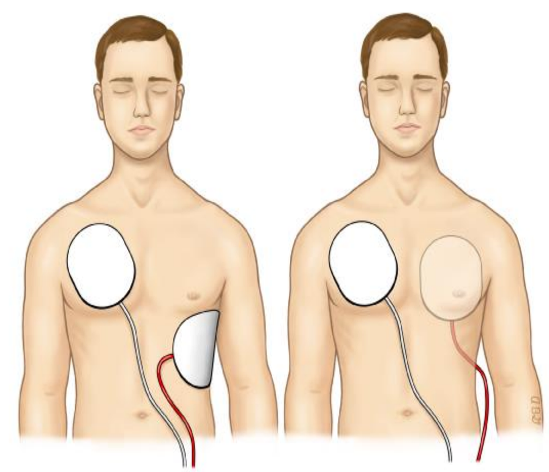
Cardioversion and Defibrillation

- **Attach ECG monitor and pulse oximeter**
- **Prepare**
  - Oxygen with preferably a facemask or nasal prong
  - Endotracheal tube
  - Laryngoscope
  - Suction machine
  - Airway adjuncts (bag-valve mask, oral and nasal airways)
  - Resuscitation medications (epinephrine, atropine, amiodarone)
  - A defibrillator with hand held paddle electrodes
- **Establish IV line**
- **Monitoring and preoxygenation**
  - BP, PR, and RR should be measured at frequent, regular intervals;
  - oxygen saturation (SpO2), and cardiac rhythm should be monitored continuously
  - Patient's level of alertness, depth of respiration, and response to painful stimuli
  - 100% oxygen should be administered for 5 to 15 minutes by nasal cannula or face mask before the procedure and continued throughout the procedure
- **Perform procedural sedation**
  - Discuss the risks, benefits, and alternatives of the procedure and the planned sedation with the patient or caretaker and answer any questions
  - **Propofol,** initial loading dose of 0.5 to 1 mg/kg IV, followed by doses of 0.5 mg/kg IV every 3-5 minutes as necessary
  - **Midazolam,** 0.5 or 1 mg at a time and titrated to effect. No single dose should exceed 2.5 mg
  - **Ketamine,** 1 to 2 mg/kg is given IV over one to two minutes. Doses of 0.25 to 0.5 mg/kg may be repeated every 5 to 10 minutes thereafter

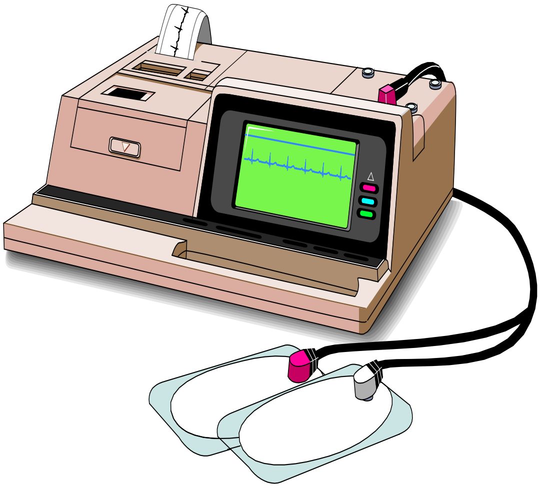
  - ***Procedural sedation may be skipped in a patient who is unstable**
- **Electrode positioning** → Pad placement
  - Sternal-apical (anterolateral) position, with the right pad placed on the right superior-anterior chest below the clavicle, and the left pad placed on the inferior-lateral left chest, lateral to the left breast

- Apply pads at least 2.5 cm away from any implantable devices
- Apply a wet gauze at the site of electrode placement

Options for hands-free pacemaker/defibrillator pad positioning



Positioning options for hands-free pacemaker/defibrillator pads showing anterior/lateral positioning (left) and anterior/posterior positioning (right).



- **Energy selection**
    - Select the appropriate energy for the specific arrhythmia
    - Press the sync button if synchronization is required
- **Clear you and your team and deliver the shock**
    - Say "I am going to shock on three. One, two, three, shocking"
    - Perform a visual check to make sure you have no contact with the patient, the stretcher or other equipment

Click on the link below and watch the video

Manual defibrillation

https://youtu.be/Dubih8EzBJQ

How to perform cardioversion and defibrillation

https://youtu.be/T7Zv9vLdWtE

1.8 Pericarditis

Classification of pericarditis

A. Classification based on duration of illness

- Acute pericarditis (<6 weeks)
  - ✓ Fibrinous
  - ✓ Effusive (serous or sanguineous)
- Subacute pericarditis (6 weeks to 6 months)
  - ✓ Effusive-constrictive
  - ✓ Constrictive
- Chronic pericarditis (>6 months)
  - ✓ Effusive
  - ✓ Constrictive
  - ✓ Adhesive (nonconstructive)

B. Etiologic Classification of pericarditis

I. **Infectious**	II. **Non infectious**
A. **Viral** (coxsackievirus A and B, echovirus, herpesviruses, mumps, adenovirus, hepatitis, HIV) B. **Pyogenic** (pneumococcus, *Streptococcus, Staphylococcus, Neisseria, Legionella, Chlamydia*) C. **Tuberculous** D. **Fungal** (histoplasmosis, coccidioidomycosis, *Candida*, blastomycosis) E. **Other** infections (syphilitic, protozoal, parasitic)	A. Acute idiopathic B. Renal failure C. Neoplasia 1. Primary tumors (benign or malignant, mesothelioma) 2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia) D. Trauma (penetrating chest wall, nonpenetrating) E. Aortic dissection (with leakage into pericardial sac) F. Acute myocardial infarction G. Post irradiation H. Familial Mediterranean fever I. Familial pericarditis 1.Mulibrey nanism J. Metabolic (myxedema, cholesterol)

III. Pericarditis presumably related to hypersensitivity or autoimmunity

A. Rheumatic fever

B. Collagen vascular disease (SLE, RA, ankylosing spondylitis, scleroderma, granulomatosis with polyangiitis [Wegener's])

C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)

D. Postcardiac injury
  1. Post pericardiotomy
  2. Posttraumatic
  3. Post myocardial infarction (Dressler's syndrome)

ACUTE PERICARDITIS

- Pericardial inflammation of < 6wks
- Acute pericarditis, by far the most common pathologic process involving the pericardium
- Can occur in a wide variety of diseases, but the majority of cases are idiopathic
- Most cases of acute idiopathic pericarditis are presumed to be viral in etiology

CLINICAL MANIFESTATIONS OF ACUTE PERICARDITIS:

- Acute pericarditis has four principal diagnostic features
  1. Chest pain
  2. Pericardial friction rub
  3. ECG features
  4. Pericardial effusion
- Chest pain present in >95%
  - ✓ The pain of pericarditis is often severe
  - ✓ Often sharp pleuritic, but can be constricting
  - ✓ It is most commonly retrosternal, but can also be centered in the left anterior chest or epigastrium
    - referred to neck arms and shoulder
  - ✓ The most characteristic radiation is the trapezius ridge, which is highly specific for pericarditis
  - ✓ Characteristically, pericardial pain intensified by lying supine, and relieved by sitting up and leaning forward
  - ✓ Associated symptoms can include dyspnea, cough, and occasionally hiccups
- Hx of an antecedent fever and URTI may suggest viral causes of pericarditis

- The differentiation of Acute MI from acute pericarditis may be challenging when, with the latter, serum biomarkers of myocardial damage such as troponin and creatine kinase-MB rise, presumably because of concomitant involvement of the epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. However, these elevations, if they occur, are quite modest compared to those in Acute MI, given the **extensive ST-segment elevation in pericarditis.**

P/E

- Uncomfortable and anxious
- Low-grade fever
- Sinus tachycardia
- Pericardial friction rub

DIFFERENTIAL DIAGNOSIS

- Pneumonia or pneumonitis with pleurisy (which may coexist with pericarditis)
- Pulmonary embolus/infarction
- Costochondritis,
- Gastroesophageal reflux disease
- MI
- Other considerations include
  - Aortic dissection
  - Intraabdominal processes
  - Pneumothorax, and
  - Herpes zoster pain before skin lesions appear

Initial Approach to the Patient with Definite or Suspected Acute Pericarditis

1. If diagnosis is suspected but not certain → check frequently for pericardial friction rub and do ECG frequently
2. If diagnosis is certain → do the following to determine etiology, associated condition and CXN
   - ✓ CXR
   - ✓ ECHO
   - ✓ CK with MB fraction, Troponin I
   - ✓ Serum ANA for young females
   - ✓ Initiate therapy with NSAID

ECG FINDINGS IN ACUTE PERICARDITIS

- ✓ Stage 1: There is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 to V_6, with reciprocal depressions only in aVR and sometimes V_1, as well as PR-segment depression. Usually there are no significant changes in QRS complexes.

- ✓ Stage 2: after several days, the ST segments return to normal
- ✓ Stage 3 :T waves become inverted
- ✓ Stage 4: ultimately, weeks or months after the onset of acute pericarditis, the ECG returns to normal

Echo

- Presence of pericardial effusion and its hemodynamic effect

MANAGEMENT OF ACUTE PERICARDITIS

- Acute idiopathic pericarditis is a self-limited disease without significant complications or recurrence in 70 to 90%
  - ✓ If lab data support acute idiopathic pericarditis symptomatic treatment with NSAID's should be initiated
- Anti-inflammatory agents
  - ○ NSAIDS: ibuprofen, ASA
  - ○ Steroids → Steroids are used if there is no response after 48hr of taking NSAID
    - ▪ Prednisone, 1-2 mg/kg/day, PO, daily or BID, for 4-6 wks, followed by gradual tapering.
    - ▪ use concurrent NSAID
  - ○ Colchicine
    - ▪ chronic +/- NSAID
    - ▪ useful in recurrent pericarditis
- Rx depending on the etiology
  - ➢ Antibiotics → purulent pericarditis
  - ➢ Anti TB → TB pericarditis

Complications of acute pericarditis

1. Pericardial Effusion
2. Cardiac Tamponade
3. Constrictive pericarditis (1%)
4. Recurrence (15-30% in idiopathic)

1. PERICARDIAL EFFUSION AND TAMPONADE

- Accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction to the inflow of blood to the ventricles results in cardiac tamponade
- It is not only the amount but the rate of fluid accumulation determines the development of cardiac tamponade

- The quantity of fluid necessary to produce this critical state may be as small as **200 mL** when the fluid develops **rapidly** or >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume

- This complication may be fatal if it is not recognized and treated promptly
- Any of cause of acute pericarditis can cause pericardial effusion and tamponade
- Those causes of effusion with a high incidence of progression to tamponade are bacterial (including mycobacteria), fungal, uremic and neoplastic involvement
- The frequency of the different causes of pericardial effusion varies in published reports

CLINICAL FEATURES

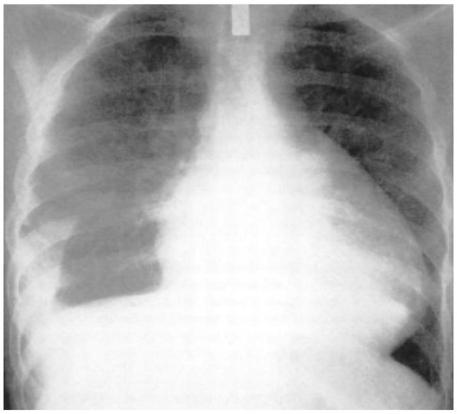
- Occasionally, large, asymptomatic chronic effusions are discovered when CXR is obtained for an unrelated reason
- Pericardial pain
- Dyspnea (in tamponade)
- **Tachycardia is the rule** unless heart rate lowering drugs have been administered, conduction system disease coexists, or a preterminal bradycardic reflex has supervened
- Apical impulse may not be palpable
- ↑ed cardiac dullness
- Friction rub may disappear
- Ewart's sign (the base of the left lung may be compressed by pericardial fluid and produce an area dullness and increased fremitus (and egophony) beneath the angle of the left scapula)
- *Beck's triad* → severe tamponade
    - Hypotension
    - Muffled heart sounds
    - Elevated JVP
- uncomfortable patient, with signs reflecting varying degrees of reduced cardiac output and shock including tachypnea; diaphoresis; cool extremities; peripheral cyanosis; depressed sensorium
- Hypotension is usually present, although in early stages compensatory mechanisms maintain the blood pressure
- A paradoxical pulse

DIAGNOSTIC APPROACH

1. ECG: low QRS voltage and electrical alternans.
2. CXR:
    - ❑ The cardiac silhouette remains normal until pericardial effusions are at least moderate in size.
    - ❑ With moderate and larger effusions, the anteroposterior cardiac silhouette

assumes a **rounded, flask like appearance**.

- ❑ The lungs characteristically appear oligemic



CXR in pericardial effusion

3. ECHO; Assess the hemodynamic impact:
4. Establish the cause: laboratory tests and pericadiocentesis and biopsy

MANAGEMENT

- ❖ Treatement of the underlying disease
- ❖ Management of cardiac tamponade
  - ➢ Fluid resuscitation
  - ➢ Fluid drainage: the choice between **open drainage** and **pericardiocentesis** is based upon local preference and experience, and upon individual patient considerations

2. CONSTRICTIVE PERICARDITIS

- ❖ It is the end stage of an inflammatory process involving the pericardium
- ❖ The result of scarring and consequent loss of elasticity of the pericardial sac
- ❖ The pathological changes are chronic inflammation, sometimes with calcification.
- ❖ Pericardium is thicker than normal in approximately 80 % of cases
- ❖ In the developed world the cause is most commonly idiopathic, postsurgical, or radiation injury
- ❖ **TB was the most common cause in in developing countries**
- ❖ Although constriction can follow an initial insult by as little as several months, it usually takes years to develop

PATHOPHYSIOLOGY

- Inability of the ventricles to fill because of the limitations imposed by the rigid, thickened pericardium

- Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole
- Despite these hemodynamic changes, myocardial function may be normal or only slightly impaired

CLINICAL MANIFESTATION

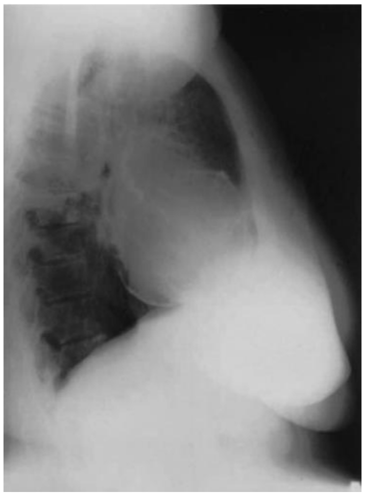
- ✓ Weakness, fatigue, weight gain, ascites and edema are common
- ✓ Chronically sick looking
- ✓ In advanced cases there are anasarca, skeletal muscle wasting, and cachexia
- ✓ Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe
- ✓ Distended neck veins
- ✓ venous pressure may fail to decline during inspiration (***Kussmaul's sign***)
- ✓ The pulse pressure is normal or reduced
- ✓ In 1/3 of the cases, a paradoxical pulse can be detected
- ✓ Congestive hepatomegaly
- ✓ Ascites is common and is usually more prominent than dependent edema
- ✓ The apical pulse is reduced and may retract in systole (*Broadbent's sign*)
- ✓ The heart sounds may be distant; an early 3rd heart sound, i.e., a pericardial knock, at the cardiac apex, it occurs with the abrupt cessation of ventricular filling
- ✓ Murmur of TR

DIFFERENTIAL DIAGNOSIS

- Restrictive cardiomyopathy
- Cardiac tamponade
- Core pulmonale
- Tricuspid stenosis

INVESTIGATIONS

- ECG:
  - Low voltage of the QRS complexes
  - Diffuse flattening or inversion of the T waves.
  - Atrial fibrillation (in about 1/3 of patients)
- CXR: shows a normal or slightly enlarged heart; pericardial calcification is most common in tuberculous pericarditis



CXR showing marked pericardial calcifications in a patient with constrictive pericarditis

- ECHO
- CT/MRI scan
- Cardiac catheterization

MANAGEMENT OF CONSTFICTIVE PERICARDITIS

- **Pericardial resection is the only definitive treatment**,
  - ✓ Dietary sodium restriction and diuretics are useful during preoperative preparation
  - ✓ Digoxin is usefull postoperatively
- Treatement of the underlying cause like tuberculosis is equally important

1.9 Cardiomyopathy (CMP) and myocarditis

A. Cardiomyopathy (CMP)

- A heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic
- CMP's Are diseases of heart muscle that result from a myriad of insults such as genetic defects, cardiac myocyte injury, or infiltration of myocardial tissues
- The term was previously reserved for primary diseases of the heart muscles, not including processes affecting valvular structures, coronary vasculature, or pericardium
- Because of the recognition of the final common pathway phenomenon, the use of the term cardiomyopathy to denote specific cardiomyopathies such as

ischemic cardiomyopathy or valvular cardiomyopathy has entered into common use

Classification

A. Etiologic classification

- ❖ Primary cardiomyopathies→ Predominantly involving the heart; Are further subdivided in to
    - ✓ Genetic
    - ✓ Acquired
    - ✓ Mixed
- ❖ Secondary cardiomyopathies → Accompanied by other organ system involvement

B. Morphologic classification

- ✓ Based on echocardiographic and autopsy findings
    - ➢ Dilated cardiomyopathy (DCMP)
    - ➢ Restrictive cardiomyopathy (RCMP) and
    - ➢ Hypertrophic cardiomyopathy (HCMP)

General presentation

- Early symptoms often relate to exertional intolerance with SOB or fatigue
- Progressive SOB
- Nocturnal cough
- Chest pain
- Peripheral oedema and ascites
- Arrhythmias
- Embolic events

IX

- ECG
- CXR
- ECHO (two-dimensional and Doppler)
- Chemistry:
    - ✓ Na, K, Ca, Mg, RBS/FBS, U/A, Creatinine and BUN, Albumin, total protein, LFT, Lipid profile, TSH, Creatine kinase, Serum iron, transferrin saturation,
- Hematology:
    - ✓ Hgb, CBC, ESR

Initial Evaluation Only in Patients Selected for Possible Specific Diagnosis

- ❖ Titers for infection in presence of clinical suspicion:
    - ➢ Acute viral (coxsackie virus, echovirus, influenza virus)
    - ➢ HIV
    - ➢ Chagas' disease

  - Lyme disease
  - Toxoplasmosis
- Catheterization with coronary angiography in patients with angina who are candidates for intervention
- Serologies for active rheumatologic disease
- Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
- Screening for sleep-disordered breathing

Table; Presentation with Symptomatic Cardiomyopathy

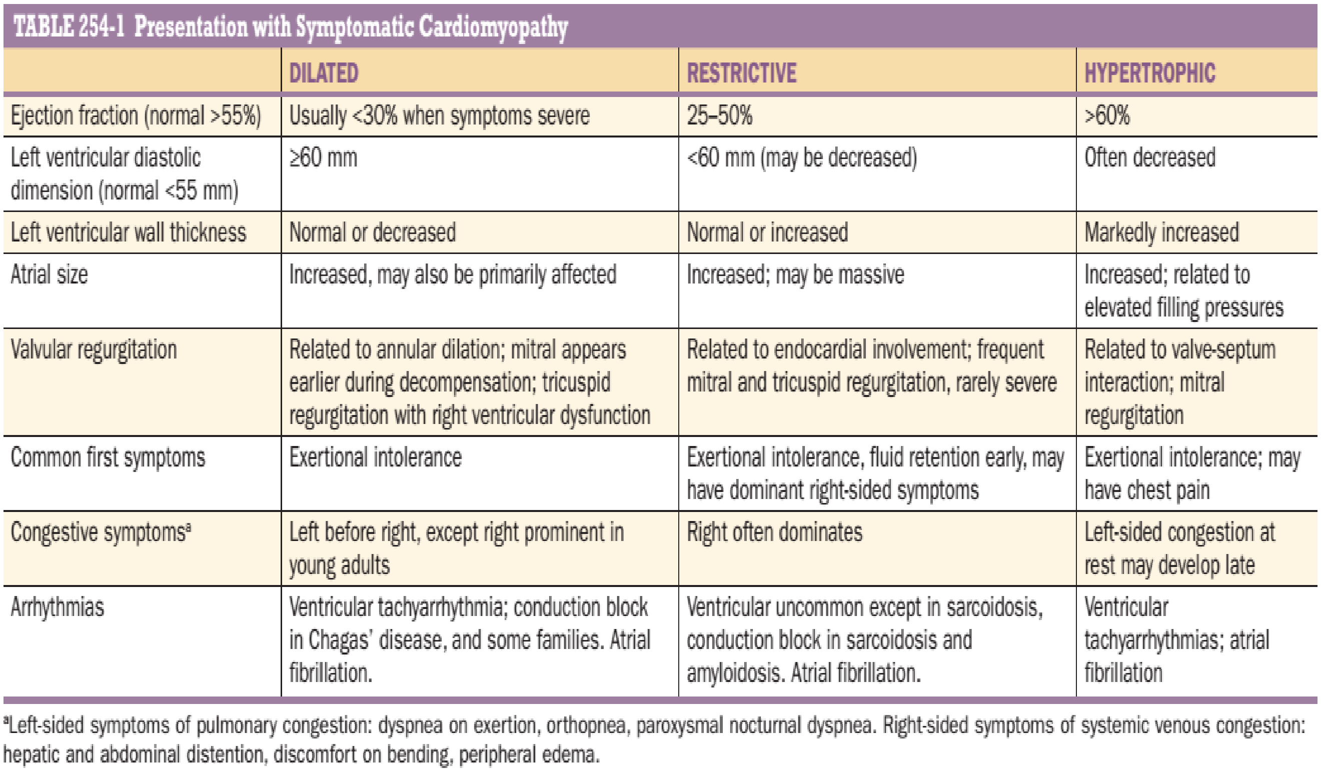


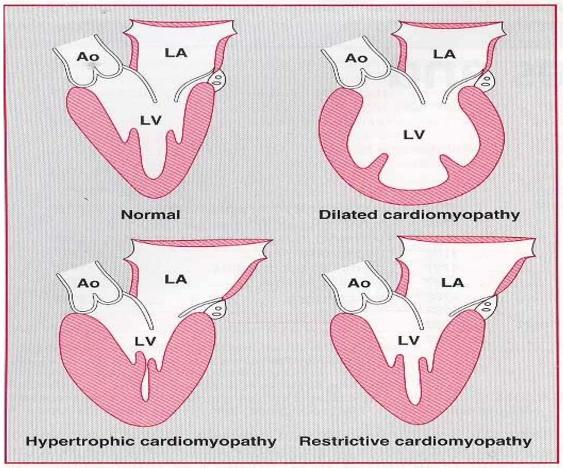
TABLE 254-1 Presentation with Symptomatic Cardiomyopathy

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased, may also be primarily affected	Increased; may be massive	Increased; related to elevated filling pressures
Valvular regurgitation	Related to annular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance; may have chest pain
Congestive symptoms[a]	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion at rest may develop late
Arrhythmias	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis, conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

[a] Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema.

Table; Investigation finding with Cardiomyopathy

	Dilated	**Restrictive**	**Hypertrophic**
Chest roentgenogram	Moderate to marked cardiac silhouette enlargement Pulmonary venous hypertension	Mild cardiac silhouette enlargement	Mild to moderate cardiac silhouette enlargement
Electrocardiogram	ST-segment and T-wave abnormalities	Low voltage, conduction defects	ST-segment and T-wave abnormalities Left ventricular hypertrophy Abnormal Q waves
Echocardiogram	Left ventricular dilatation and dysfunction	Increased left ventricular wall thickness Normal or mildly reduced systolic function	Asymmetric septal hypertrophy (ASH) Systolic anterior motion (SAM) of the mitral valve
Radionuclide studies	Left ventricular dilatation and dysfunction (RVG)	Normal or mildly reduced systolic function (RVG)	Vigorous systolic function (RVG) Perfusion defect (^{201}Tl or technetium sestamibi)
Cardiac catheterization	Left ventricular dilatation and dysfunction Elevated left- and often right-sided filling pressures Diminished cardiac output	Normal or mildly reduced systolic function Elevated left- and right-sided filling pressures	Vigorous systolic function Dynamic left ventricular outflow obstruction Elevated left- and right-sided filling pressures



1. Dilated cardiomyopathy (DCMP)

- It is the most common cardiomyopathic phenotype
- DCMP may occur at any age, it most commonly becomes apparent clinically in the 3rd or 4th decades of age

- DCMP phenotype is often viewed as a “final common pathway” of numerous types of cardiac injuries
- LV and/or RV systolic pump function is impaired, leading to progressive cardiac dilatation (remodeling)
- 1/3rd of cases are familial
- Characterized by an enlarged left ventricle with decreased systolic function
- Systolic failure is more marked than diastolic dysfunction
- MR commonly develops as the valvular apparatus is distorted and is usually substantial by the time heart failure is severe
- Dilation and decreased function of the right ventricle may result from
  - Initial injury
  - Mechanical interaction with the failing left ventricle
  - Elevated afterload presented by secondary pulmonary hypertension

Etiology

1. Idiopathic(primary)- 2/3rd of cases
2. Secondary:
   - **Post infectious** (**viral** myocarditis/ coxsackie, adenovirus, HIV, hepatitis C/, **parasitic**/ *T. cruzi*–Chagas’ disease, trypanosomiasis, toxoplasmosis/, bacterial/ diphtheria/, **spirochetal**/ *Borrelia burgdorferi*–Lyme disease)/, **Rickettsial** /Q fever/, **Fungal** /with systemic infection/)
   - Toxic (alcohol, chemotherapeutics, heavy metals)
   - Metabolic (nutritional deficiency, endocrinopathies/ Thyroid disease, Pheochromocytoma, Diabetes/, electrolyte deficiencies/ Ca, Mg, Phosphate/, obesity, hemochromatosis)
   - Peripartum cardiomyopathy
   - A reversible form of DCM may be found with alcohol abuse, pregnancy, thyroid disease, cocaine use, and chronic uncontrolled tachycardia

1.1 Peripartum cardiomyopathy (PPCMP)

- Develops within the 3rd trimester or within the first 6 months after delivery
- Risk factors
  - ✓ Increased maternal age
  - ✓ Increased parity
  - ✓ Twin pregnancy
  - ✓ Malnutrition
  - ✓ Use of tocolytic therapy for premature labor

- ✓ Preeclampsia

- ❖ Exact cause unknown
  - ✓ Cross-reactivity of anti-uterine antibodies against cardiac muscle
  - ✓ Abnormal prolactin cleavage fragments triggering myocardial necrosis
  - ✓ Increased antiangiogenic signaling

1.2 Alcoholic cardiomyopathy

- ❖ Alcohol is the most common toxin implicated in chronic DCMP
- ❖ Excess consumption may contribute to > 10% of cases of heart failure
- ❖ The alcohol consumption necessary to produce cardiomyopathy in an otherwise normal heart has been estimated to be 5-6 drinks daily for 5-10 years
  - Frequent binge drinking may also be sufficient

Treatment

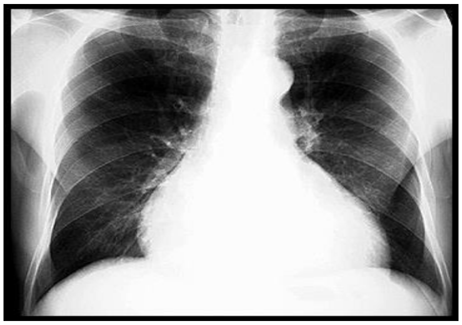
- ✓ Abstinence from alcohol
- ✓ Diuretics and neurohormonal antagonists

CLINICAL FEATURES OF DCMP

- Symptoms of left- and right-sided CHF usually develop gradually
- Some patients have LV dilatation for months or even years before becoming symptomatic
- Although vague chest pain may be present, typical angina pectoris is unusual and suggests the presence of IHD
- Syncope due to arrhythmias and systemic embolism (often emanating from a ventricular thrombus)
- Cardiomegaly and CHF findings
- Narrow pulse pressure and raised JVP (In advanced disease)
- S3 & S4 gallop
- MR & TR

INVESTIGATIONS

- ❖ CXR:
  - ✓ Enlargement of the cardiac silhouette due to LV dilatation
  - ✓ The lung fields may demonstrate pulmonary vascular redistribution and interstitial or, in advanced cases, alveolar edema



CXR; demonstrates marked enlargement of the cardiac silhouette compatible with a dilated cardiomyopathy. Cardiomegaly is nonspecific and can be seen with any etiology of cardiomyopathy.

- ECG:
  - ✓ sinus tachycardia or atrial fibrillation, ventricular arrhythmias, left atrial abnormality, low voltage, diffuse nonspecific ST-T-wave abnormalities, and sometimes intraventricular and/or AV conduction defects
- Echo, CT, & CMRI
  - ✓ show LV dilatation, with normal, minimally thickened, or thinned walls, and systolic dysfunction
- BNP level is usually elevated
- Cardiac catheterization and coronary angiography are often performed to exclude IHD

TREATEMENT OF DCMP

- Chronic anticoagulation → for the concern of Systemic embolization
- Standard therapy of HF is indicated
- Treatement of the underlying etiology whenever possible

Prognosis of DCMP

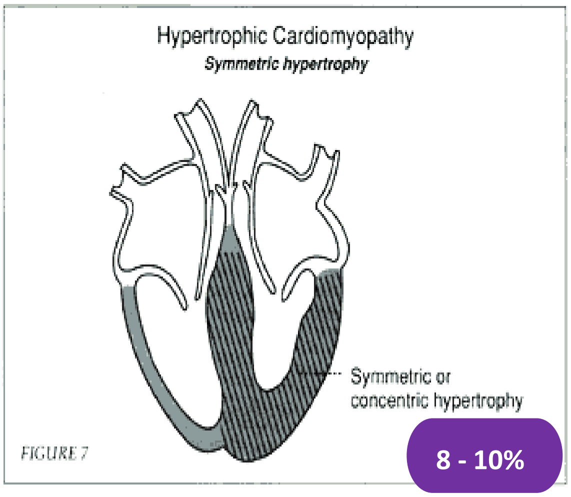
- Most patients pursue an inexorably downhill course, and the majority, particularly those >55 years, die within 4 years of the onset of symptoms
- Spontaneous improvement or stabilization occurs in about 1/4th of patients
- Patients of African ancestry are more likely to suffer more rapidly progressive CHF and death than Caucasians
- Death is due to either progressive HF or ventricular tachy- or bradyarrhythmia; **SCD is a constant threat**

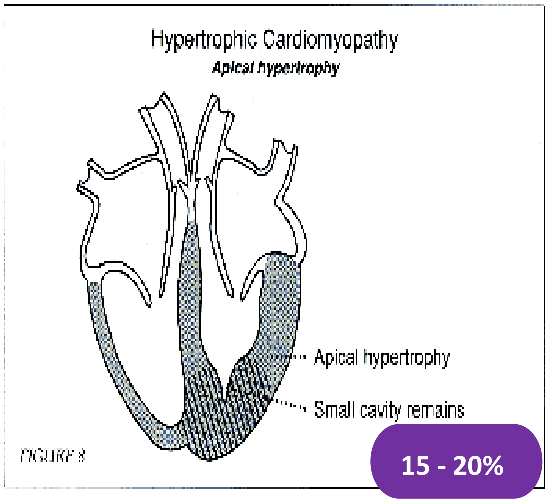
2. HYPERTROPHIC CARDIOMYOPATHY(HCMP)

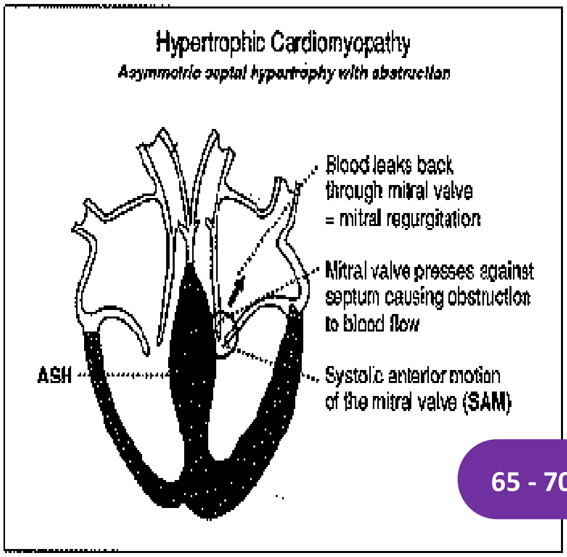
- HCM is characterized by a thickened but nondilated left ventricle in the absence of another cardiac or systemic condition capable of producing the magnitude of hypertrophy such as: HTN, AS

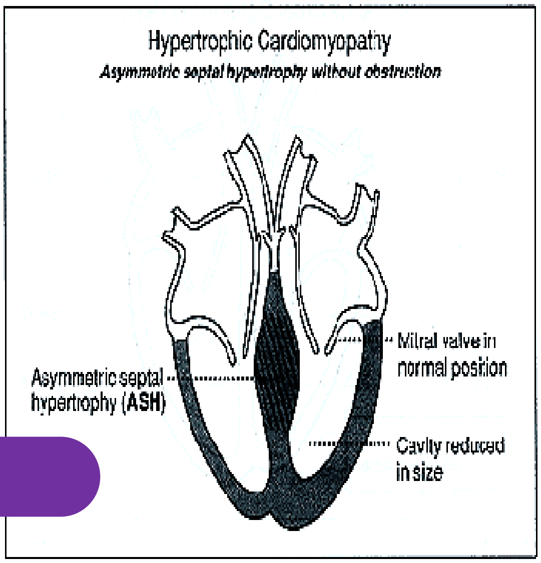
- LVH is asymmetric, often with preferential hypertrophy of the interventricular septum
  - Septal hypertrophy > LV free wall hypertrophy
- The most common of the genetic cardiovascular diseases

Variants of HCM


Hypertrophic Cardiomyopathy
Symmetric hypertrophy
Symmetric or concentric hypertrophy
FIGURE 7
8 - 10%


Hypertrophic Cardiomyopathy
Apical hypertrophy
Apical hypertrophy
Small cavity remains
FIGURE 8
15 - 20%


Hypertrophic Cardiomyopathy
Asymmetric septal hypertrophy with obstruction
Blood leaks back through mitral valve = mitral regurgitation
Mitral valve presses against septum causing obstruction to blood flow
ASH
Systolic anterior motion of the mitral valve (SAM)
65 - 70%


Hypertrophic Cardiomyopathy
Asymmetric septal hypertrophy without obstruction
Mitral valve in normal position
Asymmetric septal hypertrophy (ASH)
Cavity reduced in size

PATHOPHYSIOLOGY OF HCM

- Left ventricular outflow obstruction
  - LV outflow tract is narrowed in classic obstructive HCM by septal hypertrophy and, in some patients, by anterior displacement of the mitral valve (systolic anterior movement)

1. increased LV contractility
2. decreased ventricular preload

3. decreased aortic impedance and pressure (afterload)

- Myocardial ischemia
- Diastolic dysfunction
- Arrythmia

CLINICAL MANIFESTATIONS OF HCM

- The clinical course of HCM is highly variable
- **Many patients are asymptomatic** or mildly symptomatic and may be relatives of patients with known disease
- usually presents between the ages of **20 and 40 years**
- the first clinical manifestation may be SCD, frequently occurring during or after physical exertion
- **HCM is the most common cause of SCD in young competitive athletes**
- In symptomatic patients, the most common complaint is **dyspnea**
- Other symptoms include **syncope, angina pectoris, and fatigue.**
- Symptoms are not closely related to the presence or severity of an outflow pressure gradient
- Most patients demonstrate a **double or triple apical precordial impulse** and **S4 gallop**
- Those with intraventricular pressure gradients may have a rapidly rising arterial pulse
- The **hallmark of obstructive HCM is systolic murmur (MR, TR)**

INVESTIGATION

- ECG: LVH and widespread deep broad Q wave, tachyarrhythmias
- CXR: may be normal, mild to moderate increase in the cardiac silhouette
- ECHO:
  - demonstrates LV hypertrophy, often with the septum 1.3x the thickness of the posterior LV free wall. The septum may demonstrate an unusual "ground-glass" appearance, probably related to its myocardial fibrosis.
  - SAM of MV, often accompanied by MR, is found in patients with pressure gradients.
  - The LV cavity typically is small in HCM, with vigorous motion of the posterior wall but with reduced septal excursion

TREATEMENT OF HCM

- Since SCD often occurs during or just after physical exertion, competitive sports and very strenuous activities should be proscribed
- Dehydration should be avoided, and diuretics used with caution in

congested patients

- **Beta- blockers** drugs and verapamil
    - ✓ decrease HR and increase the length of time for diastolic filling, as well as to decrease the inotropic state
        - Amiodarone reduces frequency of arrythmias
- Diuretics, nitrates, dihydropyridine calcium blockers, vasodilators, and -adrenergic agonists are best avoided, particularly in patients with known LV outflow tract pressure gradients
- Alcohol ingestion may produce sufficient vasodilatation to exacerbate an outflow pressure gradient
- Atrial fibrillation is poorly tolerated, and a strong effort should be made to restore and then maintain sinus rhythm and slow rate
    - ✓ Beta blockers
    - ✓ Amiodarone
    - ✓ Non-dihydropyridine calcium channel blockers
    - ✓ Electrical cardioversion
- Surgical myotomy/myectomy and alcohol septal ablation can also reduce obstruction and improve symptoms
- The insertion of an ICD should be considered in patients with a high-risk profile for SCD
    - ✓ Two or more risk factors for SCD

Risk factors for SCD in HCMP

- History of cardiac arrest or spontaneous sustained ventricular tachycardia
- Syncope
- Family history of sudden cardiac death
- Spontaneous non sustained ventricular tachycardia
- LV thickness >30 mm
- Abnormal blood pressure response to exercise

3. RESTRICTIVE CARDIOMYOPATHY (RCMP)

- The hallmark of RCMP is abnormal diastolic function; the ventricular walls are excessively rigid and impede ventricular filling
- The least common of the three cardiomyopathies
- Partial obliteration of the ventricular cavity by fibrous tissue and thrombus contributes to the abnormally increased resistance to ventricular filling
- In late stages systolic function is also impaired
- Myocardial fibrosis, hypertrophy, or infiltration due to a variety of causes is responsible

Causes

- Infiltrative disorders
    - ✓ Amyloidosis
    - ✓ Storage disorders
    - ✓ Hemochromatosis
    - ✓ Inherited metabolic defects
        - Fabry's disease
        - Glycogen storage disease
- Fibrotic
    - ✓ Radiation
    - ✓ Scleroderma
    - ✓ Endomyocardial
    - ✓ Tropical endomyocardial fibrosis (EMF)
    - ✓ Hyper eosinophilic syndrome (Loffler's endocarditis)
    - ✓ Carcinoid syndrome

CLINICAL FEATURES

- Exercise intolerance and dyspnea are usually prominent
    - ✓ Thromboembolic complications are common
- Commonly have dependent edema, ascites, and an enlarged, tender, and often pulsatile liver
    - ✓ More right sided symptoms
- Kussmaul's sign is positive
- Distant heart sounds
- S4 and S3 gallop (S4 is more common than S3)

☛ **Unlike constrictive pericarditis the apex impulse is usually easily palpable, and MR is more common**

Investigations

- ✓ ECG often shows Low-voltage, nonspecific ST-T-wave abnormalities and various arrhythmias
- ✓ Echo, CTI, and CMRI typically reveal
    - Symmetrically thickened LV walls and normal or slightly reduced ventricular volumes and systolic function;
    - The atria are usually dilated
    - Intramural thrombus

☛ Differentiation of RCM from constrictive pericarditis is of importance because the latter is often curable by surgery

Treatment of RCMP

- Treatment of heart failure
    - Diuretics
    - Neurohormonal antagonists
    - Cautious use of digoxin
- Treatment of underlying causes
    - Management is usually disappointing, except for hemochromatosis and Fabry's disease
- Chronic anticoagulation is often recommended to reduce the risk of embolization from the heart
- Prognosis depends on the underlying cause

B. Myocarditis

- Myocarditis (inflammation of the heart) can result from multiple causes but is most commonly attributed infective agents that can injure the myocardium through direct invasion, production of cardiotoxic substances, or chronic inflammation with or without persistent infection.
- Classified as
    - Infectious and non-infectious myocarditis (The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection)
    - Acute, subacute and chronic myocarditis
- Infectious myocarditis has been reported with almost all types of infective agents but is most commonly associated with **viruses and the protozoan trypanosoma cruzi**
- Myocarditis is often associated with systemic inflammatory diseases, such as *polymyositis* and *dermatomyositis*, which affect skeletal and cardiac muscle.

Clinical presentation of viral myocarditis

- The typical patient with presumed viral myocarditis is **young to middle-aged** adult who develops **progressive dyspnea and weakness within a few days to weeks after a viral syndrome**
- Typical signs of CHF occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death.
- Fulminant presentation with fever, **respiratory distress, tachycardia, hypotension, gallop rhythm, and murmur** (HSM at apex)
- Cardiac findings include overactive precordial impulse, gallop rhythm, murmur of MR.
- Chest pain- due to pericardial involvement

    - Myopericarditis
    - Arrhythmias
- Pulmonary or systemic emboli

Investigation

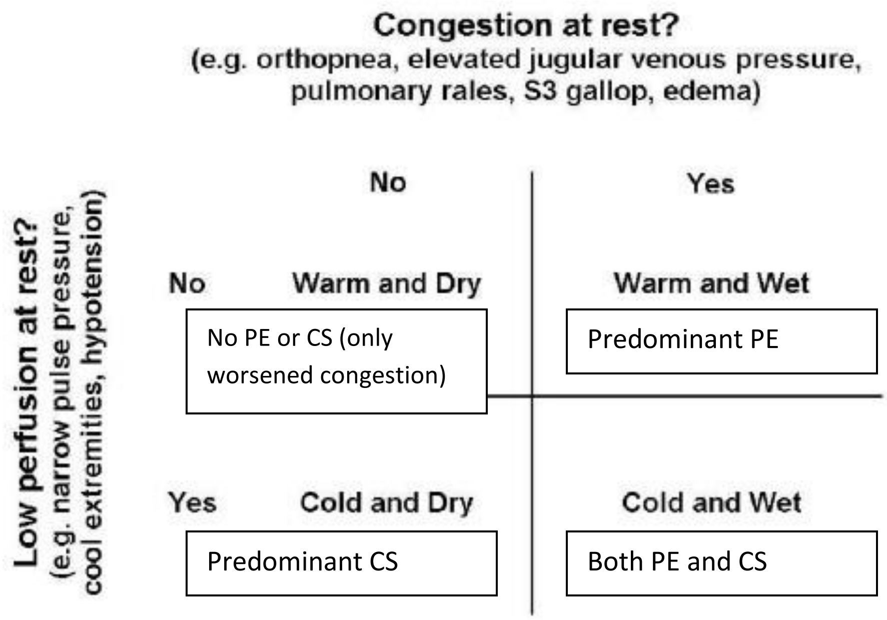
- ECG
- Echo
- Cardiac troponins
- Creatine phosphokinase
- Cardiac MRI
- Endomyocardial biopsy- indications
    - Presentation with ventricular tachyarrhythmias
    - Suspicion of alternative diagnosis such as sarcoidosis and giant cell myocarditis
- Circulating viral titers between acute and convalescent blood samples

Management

- There is currently no specific therapy recommended during any stage of viral myocarditis.
- During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury
- Benznidazole and nifurtimox which for chronic *T. cruzi* infection.
- Treatment of other infectious causes of myocarditis
- Supportive care
- Inotropic agents, preferably milrinone, should be entertained but used with caution because of their proarrhythmic potential.
- Diuretics, ACE inhibitors, and ARB's are of use in patients with compensated CHF but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse
- If significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (amiodarone) and anticoagulants should be administered and ICD placement considered.

1.10 Cardiogenic shock and Pulmonary edema

- Cardiogenic shock (CS) and pulmonary edema (PE) are life-threatening high acuity conditions that require treatment as medical emergencies, usually in an ICU or cardiac ICU (CICU).
- The most common joint etiology is severe left ventricular (LV) dysfunction from myocardial infarction (MI) that leads to pulmonary congestion and/or systemic hypoperfusion.
- These are classified based on the relative absence and/or presence of congestion and hemodynamic compromise.
- **Key Questions**
  - ✓ Does the patient have heart failure?
  - ✓ If so which syndrome among the acute heart failure syndromes?
  - ✓ Is it a new onset or worsening of a previously known cardiac disease?
  - ✓ Is there a treatable precipitating factor?
  - ✓ Does the patient require admission to the ICU or a general medical ward?



Congestion at rest?
(e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, S3 gallop, edema)

Low perfusion at rest?
(e.g. narrow pulse pressure, cool extremities, hypotension)

	No	Yes
No	**Warm and Dry** No PE or CS (only worsened congestion)	**Warm and Wet** Predominant PE
Yes	**Cold and Dry** Predominant CS	**Cold and Wet** Both PE and CS

Acute heart failure sydromes

Two-minute hemodynamic profile assessment: Patients presentation can be fitted in either of these syndromes.

Warm=good systemic perfusion

Cold=hypoperfusion (Cardiogenic shock CS=Cardiogenic shock

Dry=No lung congestion

Wet= Lung congestion (Pulmonary Edema)

PE=Pulmonary Edema

- **Factors leading to less rapid deterioration**
  - ✓ Non adherence to drugs/diet or under dosage
  - ✓ Infections (pneumonia, IE)
  - ✓ Anemia
  - ✓ Thyroid disorders
  - ✓ Pregnancy
  - ✓ Renal failure
  - ✓ Drugs (BB, CCB, NSAIDS)

- **Factors leading to rapid deterioration**
  - ✓ Tachy/brady arrhythmia
  - ✓ Acute Coronary Syndrome (ACS)
  - ✓ Acute pulmonary embolism
  - ✓ Hypertensive crisis
  - ✓ Cardiac tamponade
  - ✓ Aortic dissection

Indications for admission

Indications for admission to the ICU

- Cardiogenic shock
- Dyspnea at rest (SO_2 < 90% which doesn't improve with intranasal O_2)
- Hemodynamically significant arrhythmia
- Acute Coronary Syndrome (ACS)
- Hypertensive emergency
- Altered mental status

Indications for admission to General ward

- Worsened congestion
- Dyspnea at rest (tachypnea or SO2< 90%) which improves with intranasal O2

1.10. 1 Cardiogenic shock

➔ *Refer from Shock under short case of Nitsibin (click here → Cardiogenic shock (pump failure))*

1.10.2 Pulmonary edema

- Pulmonary edema is a term that is used to describe a particularly dramatic form of cardiogenic alveolar pulmonary edema
- It is often difficult to distinguish between cardiogenic and noncardiogenic causes of acute pulmonary edema.

Table; suggestive features to distinguish Cardiogenic from Noncardiogenic Pulmonary Edema

Cardiogenic Pulmonary Edema	Noncardiogenic Pulmonary Edema
✚ On **P/E** there is evidence of increased intracardiac pressures (S3 gallop, elevated JVP, peripheral edema), and rales and/or wheezes on auscultation of the chest. ✚ **CXR** → radiographic abnormalities typically show Kerley B lines, cardiomegaly (an enlarged cardiac silhouette), vascular redistribution, interstitial thickening, and perihilar alveolar infiltrates; pleural effusions are common. ✚ *hypoxemia* is due largely to **ventilation-perfusion mismatch** and responds to the administration of supplemental oxygen. ✚ It is most often **a result of acute decompensated heart failure (ADHF)** → usually	✚ Dominated by the findings of the precipitating condition; pulmonary findings may be relatively normal in the early stages. ✚ On CXR heart size is normal, **alveolar infiltrates** are distributed more uniformly throughout the lungs, and pleural effusions are uncommon. ✚ hypoxemia is due primarily to **intrapulmonary shunting** and typically persists despite high concentrations of inhaled O_2. ✚ **The major causes of noncardiogenic pulmonary edema are the ARDS** and, **less often, high altitude and neurogenic pulmonary edema.** Other less common causes include; ○ Pulmonary embolism

due to left ventricular systolic or diastolic dysfunction, but **may also be due to fluid overload, severe hypertension, renal artery stenosis, or severe renal disease.**	○ Eclampsia ○ Transfusion-related acute lung injury (TRALI). ○ Opioid overdose ○ DKA

- **Cardiogenic pulmonary edema** is a common and potentially fatal cause of acute respiratory distress.
    - **It is most often a result of acute decompensated heart failure (ADHF)**
    - ADHF is most commonly due to left ventricular systolic or diastolic dysfunction, with or without additional cardiac pathology, such as CAD or valve abnormalities.
    - However, a variety of conditions or events can cause cardiogenic pulmonary edema in the absence of heart disease, including primary fluid overload (e.g. due to blood transfusion), severe hypertension, renal artery stenosis, and severe renal disease.
- **Noncardiogenic pulmonary edema** is a distinct clinical syndrome associated with diffuse filling of the alveolar spaces in the absence of elevated pulmonary capillary wedge pressure
    - Noncardiogenic pulmonary edema is identified clinically by the presence of radiographic evidence of alveolar fluid accumulation without hemodynamic evidence to suggest a cardiogenic etiology (i.e. pulmonary artery wedge pressure ≤18 mmHg).
    - The accumulation of fluid and protein in the alveolar space leads to decreased diffusing capacity, hypoxemia, and shortness of breath.
    - **The major causes of noncardiogenic pulmonary edema are the acute respiratory distress syndrome (ARDS)** and, **less often, high altitude and neurogenic pulmonary edema.** Other less common causes include;
        - Opioid overdose
        - Pulmonary embolism
        - Eclampsia
        - Transfusion-related acute lung injury (TRALI).
    - Hypoalbuminemia alone is **not** a cause of pulmonary edema.
    - **Neurogenic pulmonary edema (NPE**) is one form of noncardiogenic pulmonary edema with an increase in pulmonary interstitial and alveolar fluid that is due to an acute central nervous system injury and usually develops rapidly after the injury. It is sometimes classified as a form of ARDS, but its pathophysiology and prognosis are different.

Pathophysiology

- Pulmonary edema is due to the movement of excess fluid into the alveoli as a result of an alteration in one or more of Starling's forces.
- In cardiogenic pulmonary edema, a high pulmonary capillary pressure (as estimated clinically from the pulmonary artery wedge pressure) is responsible for the abnormal fluid movement. In contrast, noncardiogenic pulmonary edema is caused by various disorders in which factors other

than elevated pulmonary capillary pressure are responsible for protein and fluid accumulation in the alveoli

- Cardiogenic pulmonary edema is characterized by increased transudation of protein-poor fluid into the pulmonary interstitium and alveolar spaces.
- The primary etiologic factor is a rapid and acute increase in left ventricular filling pressures and left atrial pressure, usually associated with a reduction in cardiac output.

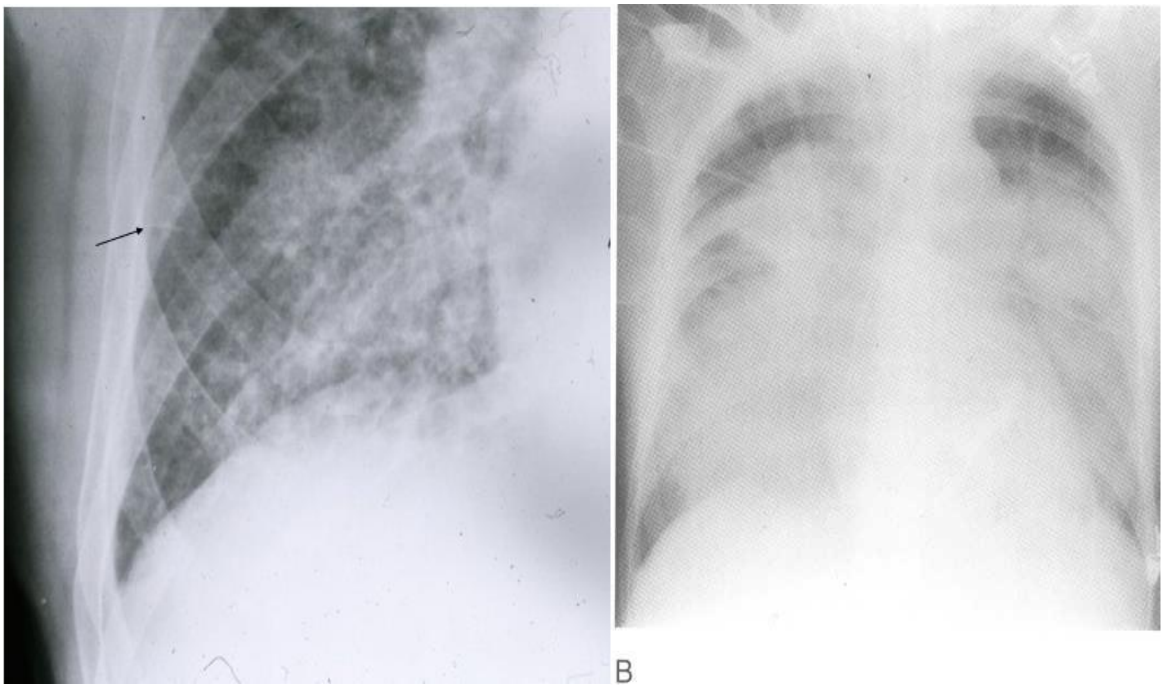
Clinical features

- Acute pulmonary edema usually presents with the
    - **Rapid onset of dyspnea at rest**
    - **Tachypnea**
    - **Tachycardia, and**
    - **Severe hypoxemia** ($SO2< 90\%$).
- Other features include;
    - **Cardiorespiratory distress**
    - High/normal BP
        - Hypertension is due to release of endogenous catecholamines.
    - **Relative dullness**
    - Decreased air entry
    - Fine crepitations **(Bilateral basal rales)** and wheeze in the lung
        - **Crackles and wheezing** due to alveolar flooding and airway compression from peribronchial cuffing may be audible.
    - Raised JVP
    - S3 gallop

Diagnosis

- **Chest X-ray → CXR finding of pulmonary edema**
    - **Vascular redistribution:** cephalization of the vessels (Diversion of Blood vessel circulation towards the Apex)
    - **Interstitial edema,** peribronchial cuffing, and Kerley B and A lines.
        - Kerley B lines: seen at the peripheral lung; due to thickened interlobular septa.
        - Kerley A lines radiate outward from the hila and may represent dilation of lymphatic channels.
    - **Alveolar edema**
        - Bilateral perihilar opacifications
        - Bat wing/butterfly appearance when severe
        - Pleural effusions and cardiomegaly are often present.

Note: pulmonary edema is usually symmetric and dependent



Picture; A) Kerley B lines (black arrow); Tiny horizontal lines seen at the periphery of the basal lung area, perpendicular to the pleura…represent fluid in the interlobular septa. B) PA CXR: typical batwing distribution of air space disease

- *Echo* → may identify systolic and diastolic ventricular dysfunction and valvular lesions.
- ECG → ST elevation and evolving Q waves are usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery revascularization therapy.
- BNP → when substantially elevated, support heart failure as the etiology of acute dyspnea with pulmonary edema.

Treatment of pulmonary edema

- The treatment of pulmonary edema depends on the specific etiology.
- As an acute, life-threatening condition, a number of measures must be applied immediately to support the circulation, gas exchange, and lung mechanics.
- Simultaneously, conditions that frequently complicate pulmonary edema must be corrected such as
    - Infection
    - Acidemia
    - Anemia
    - AKI
- Treatable precipitating causes (e.g. hypertensive crisis, ACS, arrhythmia like AF) should be looked for and managed promptly

- *Physical Methods*
    - In no hypotensive patients, venous return can be reduced by use of **the sitting position** with the legs dangling along the side of the bed.
- **Oxygen Therapy**
    - Early oxygenation and ventilation support are lifesaving
    - Generally, the goal is O2 saturation of ≥92%, but very high saturation (>98%) may be detrimental.
    - Oxygen should be given in Sitting position
    - If SO_2< 90%, administer O2 by nasal canula at 4-6 l/min.
    - If SO_2 doesn't improve in 10 min, administer high flow O2(10-12 l/min) by face mask.
    - If SO_2 is still low, give ventilator support by CPAP in conscious cooperative patients or intubate if patient cannot protect his /her airways and put on MV with low PEEP.
    - If SO_2 is persistently higher than 90% and cardiorespiratory distress improves with treatment, revert O_2 administration to nasal canula and progressively decrease O_2 flow and discontinue
- Administer **morphine** 2-4 mg IV bolus every 2-4 hr.
- **Furosemide 40mg IV** for naïve (intravenous dose which is equal to their previous oral dose for those already taking oral furosemide) and **double the dose every 1hr until adequate urine output** AND **crackles in the chest start to decrease** and **maintain** the dose of furosemide that gave adequate response **every 4hrs for the first 24 hr** and decrease frequency in subsequent days.

☛ Follow up of response and other management principles are similar to management of other heart failure syndromes (*click here* → Management of heart failure)

For patients not responding adequately to diuretics with systolic BP >110mmHg, the following vasodilator therapies can be used:

- Sublingual nitroglycerin (0.4 mg × 3 every 5 min) is first-line therapy for acute cardiogenic pulmonary edema.
- If pulmonary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin.
- **IV nitroglycerine infusion**
    - 10 to 20 μg/minute, with subsequent titration (eg, 10 to 20 μg/minute every 5 to 15 minutes) up to 200 μg/minute **or**
    - 0.3 to 0.5 μg/**kg**/minute with titration (if SBP ≥90 mm Hg) in increments of 20 μg/minute every 1 to 3 minutes up to 400 μg/minute.
    - Patients who do not respond hemodynamically with doses of ~200 μg/minute should be considered non-responders
- **If nitroglycerine not available**, either of the following can be tried.
    - ✓ **Isosorbide dinitrate** 10mg, PO, TID (8AM, 1PM and 6PM) escalated

to 40mg PO TID *or*

- ✓ **Captopril** 6.25mg to 12.5 mg, PO, TID (target dose; 50mg TID) **or**
- ✓ **enalapril** 2.5 mg, PO, BID, titrated every 6hrs as tolerated to target dose of 10 mg, PO, BID (maximum: 20 mg/day).
- ✓ **Notice;** ACE inhibitors reduce both afterload and preload and are recommended for hypertensive patients.

1.10.2.1 ARDS (Acute respiratory distress syndrome)

- Acute respiratory distress syndrome (ARDS) is a **clinical syndrome** of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates **leading to respiratory failure.**
- ARDS is caused by diffuse lung injury from many underlying medical and surgical disorders.
- The lung injury may be direct, as occurs in toxic inhalation, or indirect, as occurs in sepsis.
- ARDS is defined by three categories based on the degrees of hypoxemia. These stages of mild, moderate, and severe ARDS are associated with mortality risk and with the duration of mechanical ventilation in survivors.
- **Previously** it was called **shock lung**, **adult respiratory distress syndrome**. Subsequent recognition that individuals of any age could be afflicted led to the current term, acute respiratory distress syndrome (ARDS).
- **Clinical hallmarks** of ARDS are **hypoxemia and bilateral radiographic opacities**, while the pathological hallmark is diffuse alveolar damage (i.e. alveolar edema with or without focal hemorrhage, acute inflammation of the alveolar walls, and hyaline membranes).
- ARDS is associated with a variety of risk factors and etiologies. These conditions are grouped together under the term ARDS because the clinical, physiological features, pathological features, and management are similar regardless of the inciting event.

Etiologies and predisposing factors

More than 60 possible causes of ARDS have been identified and other potential causes continue to emerge as adverse pulmonary reactions to new therapies are observed

Table; list of conditions associated with ARDS

1. **Sepsis → the most common cause of ARDS**
2. **Aspiration**
3. **Infectious pneumonia**
4. **Severe trauma**
5. **Pulmonary contusion**
6. **Multiple fractures**
7. **Amniotic fluid embolism**
8. **Neurogenic pulmonary edema**
9. **Surface burns**
10. Multiple blood transfusions → **Transfusion-related acute lung injury (TRALI)**
11. Following **upper airway obstruction**
12. Venous air embolism
13. Drugs and alcohol → Drug overdose and drug reactions
14. Leucoagglutinin reactions
15. Acute Pancreatitis
16. Near drowning
17. Smoke inhalation
18. Cardiopulmonary bypass
19. Following bone marrow transplantation
20. Acute eosinophilic pneumonia*
21. Bronchiolitis obliterans organizing pneumonia (BOOP)*
22. Miliary tuberculosis*
23. Other risk factors
    - ✓ cigarette smoking
    - ✓ cardiopulmonary bypass
    - ✓ thoracic surgery
    - ✓ pneumonectomy
    - ✓ obesity
    - ✓ blood type A

*Specific treatment required

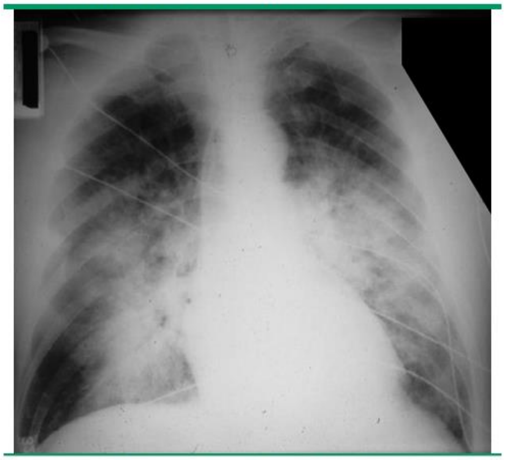
CLINICAL FEATURES

- ✓ The clinical features of ARDS usually appear within 6 to 72 hours of an inciting event and worsen rapidly.
- ✓ Patients typically present with;
    - o Dyspnea
    - o Cyanosis (i.e. hypoxemia)
    - o Diffuse crackles.
        - ✓ The bilateral alveolar infiltrates and diffuse crackles are persistent
    - o Respiratory distress is usually evident, including tachypnea, tachycardia, diaphoresis, and use of accessory muscles of respiration.
    - o A cough and chest pain may also exist.
- ✓ Clinical findings related to the precipitant may also exist at presentation. As an example, in patients with ARDS due to sepsis, there may be fever, hypotension, leukocytosis, lactic acidosis, and DIC.

Investigations

- ➢ **Sepsis work up** based on septic focus → CBC, ESR and CRP, U/A, S/E, Culture, CXR
- ➢ **CXR** → The initial chest radiograph typically has bilateral alveolar infiltrates

Acute respiratory distress syndrome



Chest radiograph showing diffuse, bilateral, alveolar infiltrates without cardiomegaly in a patient with ARDS.

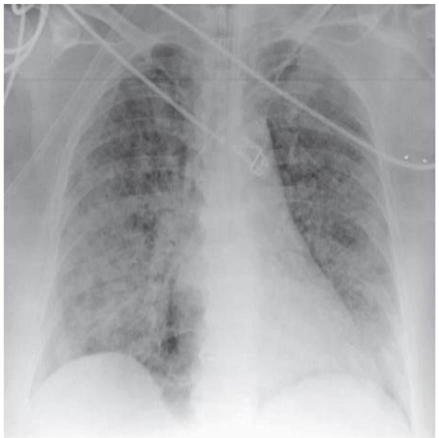


FIGURE 294-2 A representative anteroposterior chest x-ray in the exudative phase of ARDS shows bilateral opacities consistent with pulmonary edema that can be difficult to distinguish from left ventricular failure.

- **Chest CT** → usually reveals widespread patchy or coalescent airspace opacities that are usually more apparent in the dependent lung zones. The infiltrates do not have to be diffuse or severe, as bilateral infiltrates of any severity are sufficient.

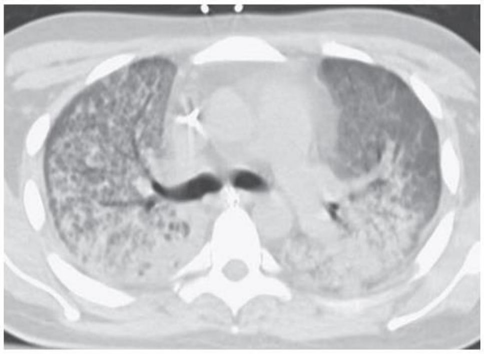
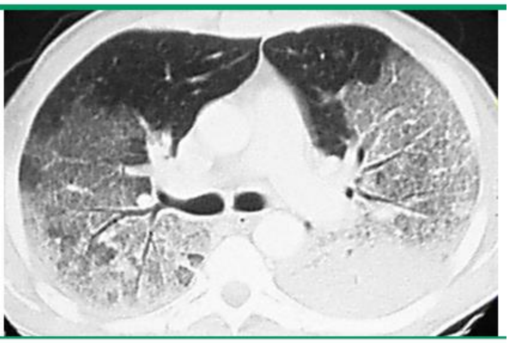


FIGURE 294-4 A representative CT scan of the chest during the exudative phase of acute respiratory distress syndrome (ARDS), in which *dependent* alveolar edema and atelectasis predominate.

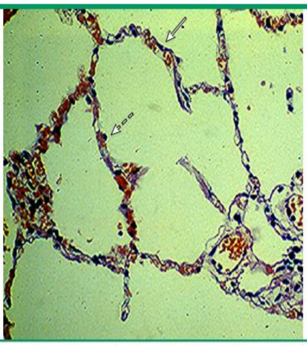
ARDS CT



ARDS due to sepsis after pneumococcal pneumonia.

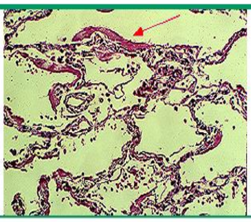
- **ABG analysis** → Arterial blood gases reveal hypoxemia, which is often accompanied by acute respiratory alkalosis and an elevated alveolar-arterial oxygen gradient. High concentrations of supplemental oxygen are generally required to maintain adequate oxygenation.
- **Microscopic (pathologic) evaluation** → lower respiratory samples can be taken by
  - **Flexible bronchoscopy**
  - **Lung biopsy** → **it** should be reserved for carefully selected patients whose acute hypoxemic respiratory failure remains of uncertain etiology after nondiagnostic flexible bronchoscopy if one or more of the diagnostic possibilities under consideration might warrant targeted therapy or would substantially change the prognosis. Examples include cryptogenic organizing pneumonia, an acute fungal lung infection, an acute exacerbation of a chronic interstitial lung disease, vasculitis, or disseminated cancer.

Normal lung



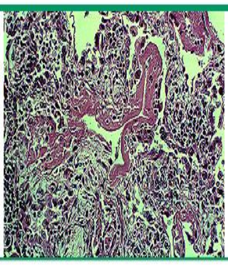
High power photomicrograph shows alveoli containing capillaries within a narrow interstitium. The alveoli are lined with thin, elongated type I pneumocytes (arrow) and smaller numbers of cuboidal type II pneumocytes (dashed arrow).

Early diffuse alveolar damage



Photomicrograph shows early diffuse alveolar damage with minimal alveolar septal thickening, hyperplasia of pneumocytes, and eosinophilic hyaline membranes (arrow).

Late diffuse alveolar damage

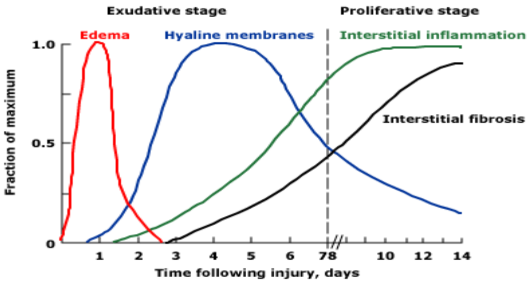


High power photomicrograph shows changes typical of the proliferative or late stage of diffuse alveolar damage. Although hyaline membranes are still identifiable, the histologic picture is now dominated by thickening and reorganization of interstitial structures due mainly to marked proliferation of mesenchymal spindle cells, including both fibroblasts and myofibroblasts.

Clinical course and pathologic stages

- Diffuse alveolar damage (DAD) is the most common pathologic finding seen in patients with ARDS.
    1. **"acute/exudative phase →** Common findings during the first week include eosinophilic hyaline membranes, intra-alveolar edema, congestion of the capillaries, widening of the interstitium, and extensive thrombi caused by localized coagulation abnormalities
    2. **Proliferative phase →** Later findings include expansion of the interstitium with loose, myxoid fibroblastic tissue, type 2 pneumocyte hyperplasia, squamous metaplasia, thrombi, and vascular remodeling. Some patients progress to a **fibrotic stage,** characterized by obliteration of normal lung architecture, diffuse fibrosis, and cyst formation.

Time course of acute respiratory distress syndrome (ARDS)



Schematic representation of the time course of the acute respiratory distress syndrome (ARDS). During the early (or exudative) phase, the lesion is characterized by high permeability pulmonary edema followed by the formation of hyaline membranes. After seven to ten days, a proliferative phase may develop, with marked interstitial inflammation, fibrosis, and disordered healing.

DIAGNOSTIC EVALUATION

- The diagnostic evaluation is aimed at identifying specific causes of ARDS that are amenable to treatment and excluding other conditions that also present with acute hypoxemia, bilateral alveolar infiltrates, and respiratory distress.
- Because the current international consensus definition of ARDS (see 'Diagnostic criteria' below) specifies no criteria relating to the underlying etiology of acute bilateral inflammatory lung injury, some uncertainty remains

with respect to which conditions should or should not be included under the ARDS diagnostic umbrella.

- Generally included are disorders that are known to cause diffuse alveolar damage and have the potential to resolve over time.
- Thus, viral or diffuse bacterial pneumonia and acute inhalational injuries are included, whereas eosinophilic pneumonia and diffuse alveolar hemorrhage associated with collagen vascular diseases are not.
- **R/o Cardiogenic pulmonary edema**
  - It is the primary alternative that needs to be excluded because it is common and can be clinically indistinguishable from ARDS.
  - See clinical features from the table above (Distinguishing features of Cardiogenic from Noncardiogenic Pulmonary Edema) → Absence of these features helps distinguish ARDS from cardiogenic pulmonary edema
  - Distinguishing cardiogenic pulmonary edema from ARDS can be aided by measurement of a brain natriuretic peptide (BNP) level, echocardiography, and, less often, right heart catheterization.
- Excluding other causes of hypoxemic respiratory failure

DIAGNOSTIC CRITERIA (Berlin definition)

- ARDS can be diagnosed once cardiogenic pulmonary edema and alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates have been excluded.
- The Berlin Definition of ARDS requires that all of the following criteria be present to diagnose ARDS:
  - Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week.
  - Bilateral opacities consistent with pulmonary edema must be present on a CXR or CT. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.
  - The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (eg, echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present.
  - A moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS based on ABG analysis:
    - **Mild ARDS** — The PaO_2/FiO_2 is >200 mmHg, but ≤ 300 mmHg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O.
    - **Moderate ARDS** — The PaO_2/FiO_2 is >100 mmHg, but ≤ 200 mmHg, on ventilator settings that include PEEP ≥ 5 cm H_2O.
    - **Severe ARDS** — The PaO_2/FiO_2 is ≤ 100 mmHg on ventilators setting that include PEEP ≥ 5 cm H_2O.
- The Berlin Definition of ARDS replaces the American-European Consensus Conference's definition of ARDS.
  - The major changes to the Berlin Definition are that the term "acute lung injury" has been eliminated, the pulmonary capillary wedge

pressure (ie, pulmonary artery occlusion pressure) criterion has been removed, and minimal ventilator settings have been added.
  - Despite these definitions, studies suggest that ARDS, in particular mild ARDS, remains under recognized by clinicians.

Table; Diagnostic Criteria for ARDS		
Severity; oxygenation*	*Mild:*	200 mmHg $<$ Pao2/Fio2 $\le$ 300 mmHg
	Moderate:	100 mmHg $<$ Pao2/Fio2 $\le$ 200 mmHg
	Severe:	Pao2/Fio2 $\le$ 100 mmHg
Onset		**Acute: Within 1 week of a clinical insult or new or worsening respiratory symptoms.**
CXR		**Bilateral opacities consistent with pulmonary edema** not fully explained by effusions, lobar/lung collapse, or nodules
Absence of left atrial hypertension		Hydrostatic edema is not the primary cause of respiratory failure. If no ARDS risk factor is present, then some objective evaluation is required (e.g., echocardiography) to rule out hydrostatic edema
*As assessed on at least 5 cm H_2O of positive end expiratory pressure (PEEP). *Abbreviations:* ARDS, acute respiratory distress syndrome; Fio2, inspired O2 percentage; Pao2, arterial partial pressure of O2; PCWP, pulmonary capillary wedge pressure.		

DIFFERENTIAL DIAGNOSIS

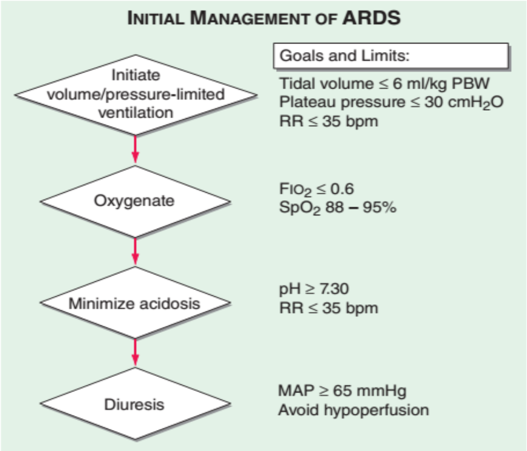
1. Cardiogenic pulmonary edema
2. An acute exacerbation of idiopathic pulmonary fibrosis or other chronic ILD
3. Diffuse alveolar hemorrhage
4. Idiopathic acute eosinophilic pneumonia (IAEP)
5. Cryptogenic organizing pneumonia (COP)
6. Acute interstitial pneumonia (Hamman-Rich syndrome)
7. Metastatic Cancer to lung

Management

- **ABC of life and Supportive management**
  - *Prone Positioning*
  - A minority of patients with ARDS die from respiratory failure alone. More **commonly**, such patients succumb to their **primary illness** or to secondary complications such as **sepsis or multiorgan system failure**
  - **Management of hypoxia →** By definition, patients with ARDS are severely hypoxemic. Options available for improving arterial oxygen saturation (SaO_2) include:
    - ✓ Oxygen supplementation
    - ✓ Intubation and mechanical ventilation
  - Patients with ARDS require meticulous supportive care, including;
    - ✓ ICU admission for severe cases
    - ✓ Prone positioning (bed elevation)→ improves oxygenation in the majority of patients with ARDS

- ✓ Nursing care and positioning for critically ill patients
- ✓ Intelligent use of sedatives and neuromuscular blockade
    - ▪ Patients with severe ARDS may require sedation for several days or longer
    - ▪ choice of agent should be driven by the patient's specific needs. For example, **narcotics** may be used for **pain and suppression of the respiratory drive**; benzodiazepines may be used for anxiety; and antipsychotic agents may be helpful for agitated delirium
    - ▪ All these agents have potential side effects which needs evaluation with specialist (if available, pneumonologist intervention is required)
- ✓ analgesics → Morphine
- ✓ hemodynamic management
- ✓ nutritional support
- ✓ control of blood glucose levels
- ✓ expeditious evaluation and treatment of nosocomial pneumonia
- ✓ prophylaxis against deep DVT and GI bleeding.
    - ▪ These patients often have multiple **risk factors for venous thrombosis**, including **prolonged immobility, trauma, activation of the coagulation pathway**, and predisposing illnesses, such as **sepsis, obesity, and malignancy**. Thus, all patients admitted to intensive care units require some form of thromboprophylaxis
    - ▪ **Stress ulcer prophylaxis → Oral PPI (like omeprazole, pantoprazole)** for critically ill patients **who are able to receive enteral medications**, Oral PPI or H2 blockers (like cimetidine) for critically ill patients who cannot receive enteral medications

- **Pharmacologic management**
    - ○ **Lasix** for pulmonary edema → look at above
        - ✓ Conservative strategy of fluid management in patients with ARDS, as long as hypotension and organ hypoperfusion can be avoided
    - ○ **Macrolides** like azithromycin, erythromycin have a beneficial effect in ARDS
    - ○ **Aspirin** has been studied as **a preventative agent** in patients with ARDS. However, **no role for it in the treatment of ARDS**
    - ○ **Systemic glucocorticoids** should be administered to patients when ARDS has been precipitated by a steroid-responsive process (eg, acute eosinophilic pneumonia) or in patients in whom steroids have a proven role (eg, community acquired pneumonia). However, their administration to patients with ARDS from other causes is controversial
        - ✓ N.B Patients who received glucocorticoids prior to the onset of ARDS associated with higher mortality
- **Early detection and treatment of complications**


INITIAL MANAGEMENT OF ARDS
Initiate volume/pressure-limited ventilation
Goals and Limits:
Tidal volume ≤ 6 ml/kg PBW
Plateau pressure ≤ 30 cmH2O
RR ≤ 35 bpm
Oxygenate
FIO2 ≤ 0.6
SpO2 88 – 95%
Minimize acidosis
pH ≥ 7.30
RR ≤ 35 bpm
Diuresis
MAP ≥ 65 mmHg
Avoid hypoperfusion

Figure; Algorithm for the initial management of ARDS. Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill patients with ARDS.
FiO_2, inspired O_2 percentage; MAP, mean arterial pressure; PBW, predicted body weight; RR, respiratory rate; SPO_2, arterial oxyhemoglobin saturation measured by pulse oximetry.

Complications

- Complications related to mechanical ventilation
    - Pulmonary barotrauma
    - nosocomial (Hospital acquired) pneumonia → it is an important complication among patients with ARDS and can contribute to increased morbidity, including prolonged mechanical ventilation
- Complications related to critical illness and being in the ICU
    - Delirium
    - DVT
    - GI bleeding due to stress ulceration
    - Catheter-related infections.
    - Poor nutrition

Prognosis and outcomes

- ARDS is associated with appreciable mortality, with estimates ranging from 26 to 58%. Mortality increases with disease severity.
- The underlying cause of the ARDS is the most common cause of death among patients who die early. In contrast, **nosocomial pneumonia and sepsis are the most common causes of death among patients who die later in their clinical course.** Patients uncommonly die from respiratory failure
- **Predictors of death**
    - **Patient-related** → The mortality rate **increased progressively with age**, ranging from 24% among patients 15 to 19 years of age to 60% among patients 85 years of age or older. **obesity** may impact the mortality
    - **Disease-related** predictors of mortality include **severe hypoxemia, failure of oxygenation to improve, pulmonary vascular dysfunction, increased dead space, infection, a high severity of illness score, a non-traumatic cause** of the ARDS, and certain biomarkers and gene polymorphisms.

- **Treatment-related** predictors of mortality which may be associated with higher mortality include;
    - ✓ **Positive fluid balance**
    - ✓ Patients who received **glucocorticoids prior to the onset of ARDS**
    - ✓ Patients who receive **packed red blood cell transfusions**
    - ✓ Patients who are **intubated late** in the course of the disease

Chapter 2; Cor pulmonale and Chronic lung disorders

Dr. Mulualem. G, Dr. Asmare.W

- N.B the approach (Hx, P/E, IX, DDX…) we discussed here is considering Cor pulmonale 2ry to COPD. If you have a patient with different diagnosis (e.g. COPD only, Cor pulmonale 2ry to Post TB fibrosis…), you can modify this approach.

Cor pulmonale

- The symptoms in chronic Cor pulmonale generally are related to the underlying pulmonary disorder.
- In our set up, Cor pulmonale patients usually have longstanding COPD or TB (e.g. Post TB fibrosis…) then they develop Cor pulmonale (isolated RSHF) smx
- They may present with
    - **Dyspnea or Exacerbation of SOB → the most common symptom**
    - **Lower-extremity edema** and even increased abdominal girth due to ascites, even may progress to GBS (Generalized body swelling)

For example

- SOB Of 2 years duration associated with productive cough with sputum production. The Patient diagnosed to have TB, Treated and improved. Currently presented with exacerbation of SOB of two weeks duration and GBS of one-week duration (characterize GBS in detail) but no orthopnea, PND or palpitation (absence of these symptoms suggests isolated RSHF) *(refer CHF of Nitsibn for GBS characterization)*

COPD (Chronic obstructive lung disease)

Clinical features and how to write hx of COPD patient

History

- COPD patients may present with
    - Exacerbation of SOB
    - Chronic cough
- **The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea.**
    - Many patients have such symptoms for months or years before seeking medical attention any may present with exacerbations
    - From the three, *the most common early symptom is exertional dyspnea. Less common symptoms include wheezing and chest tightness.*
- Chronic cough → a.k.a smoker's cough
    - The cough is intermittent early in the morning at the beginning which progressively become persistent throughout the day, but is seldom entirely nocturnal.
    - Aggravated by dust and increase in intensity and frequency at night
- Sputum production
    - Sputum initially occurs in the morning but later will be present all day long.
    - It is usually tenacious and mucoid and in small quantities. Clear, whitish, yellow or greenish (change in sputum color usually to purulent suggest infectious exacerbation)
    - Usually tenacious and mucoid
    - Massive in amount which increase progressively in amount
    - Initially occur in the morning latter occur throughout the day
    - Usually abnormal → a mix of saliva and mucus in the airway
- SOB (dyspnea, breathlessness) → daily activities can become very difficult as the condition gradually worsens
    - Insidious in onset
    - Progressively worsening (e.g he/she experienced Dyspnea while doing supra ordinary activities like…. Followed by dyspnea while doing sub ordinary activities like… and later dyspnoea at rest… when was the time for each)
    - Aggravated by excessive cigarette smoking, adverse atmospheric condition, infection…
    - *Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for many patients with COPD. Conversely, activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated. Examples of such activities include pushing a shopping cart or walking on a treadmill.*

- *As COPD advances, the principal feature is worsening dyspnea on exertion with increasing intrusion on the ability to perform vocational or avocational activities.*
- *In the most advanced stages, patients are breathless doing simple activities of daily living.*
- *Patients may also develop resting hypoxemia and require institution of supplemental oxygen.*

N.B Common variants of COPD

Chronic bronchitis	Emphysema
✓ Cough and sputum production for at least 3 months in at least 2 consecutive years ✓ Predominant productive cough ✓ Clinical definition and Dx of exclusion	✓ Permanent Dilatation of the Airway below terminal bronchiole with alveolar wall destruction. ✓ Predominant SOB ✓ Pathologic definition

- ➢ Wheezing
- ➢ Chest tightness (squeezing chest pain or chest discomfort which exacerbated by exertion but no radiation)
- ➢ Recurrent respiratory infections (cough, runny nose, sore throat, fever…) → risk factor for exacerbation
- ➢ GBS if they develop Cor pulmonale.

Risk factors for COPD

Exposure

- ➢ Cigarette smoking or Environmental tobacco smoke (ETS)
  - ✓ At least 10-20 pack year
    - ❖ $$pack\ year = \frac{(number\ of\ cigarette\ smoked\ per\ day)\ x\ (number\ of\ years\ he\ or\ she\ smoked)}{20}$$
    - ❖ One pack of cigarette contain 20 cigarettes
  - ✓ Accounts for 85-90% of all cases of COPD → 10-20 % of smokers will develop COPD & from COPD patients 80-90% are smokers which is related to genetic and environmental factors
  - ✓ The most common risk factor in westerns for both emphysema and chronic bronchitis
- ➢ Air pollution→ indoor or outdoor air pollution
  - ✓ Indoor air pollution
    - Common risk factor in our setup
    - In our setup the most common cause is poor ventilation of house and indoor smoke produced by biomass fuel combustion and dust exposure during house cleaning in rural areas (especially in women)

        - 90% of rural household use biomass fuel as a source of energy (wood, charcoal, vegetable and plant matter, animal dung)
        - In developing countries 50% of COPD death is from biomass smoke and 75 % are female
    - ✓ Outdoor air pollution → also contributes to the lungs total burden of inhaled particles, although it appears to have a relatively small effect in causing COPD.
- Occupational exposure → High risk groups include factory workers, coal mining, cotton textile industry…
    - Exposure to organic and inorganic dusts, chemicals agents and fumes
    - Inhaled irritants (direct chemical inhalation) such as cadmium, isocyanates, and fumes result in sudden airway constriction
- Respiratory infection → they are the cause of acute exacerbation. E.g. acute bronchitis
- Low socioeconomic status
    - Its association with Risk of COPD is not clear. However, this pattern may be related to indoor and outdoor air pollution, crowding, poor nutrition, infections or other factors related to low socioeconomic status.

Host Factors

- Genetic factors → alpha1 antitrypsin (AAT) deficiency especially for emphysema. N.B AAT act against lung parenchyma destructive enzymes (protease/elastase/ and trypsin)
- Asthma and airway hyper responsiveness
- Old age (Age > 65)
    - **Over all, aging increase COPD risk.** In our set up COPD can happen in < 65 years old (we didn't get data about age and COPD association in Ethiopia, what we observed during our clinical attachment is, most of COPD patients are old age and usually females)
- Gender → common in females, may be associated with high risk of exposure from indoor pollution
- Lung Growth and development
    - Any factor that affect lung growth during pregnancy and childhood (E.g. Low birth weight, neonatal meconium aspiration syndrome, respiratory infections) has the potential to increase an individual's risk of developing COPD during adult hood

Complication of COPD

- Cxn related to emphysema
    - ✓ Respiratory insufficiency

  - ✓ Respiratory failure (N.B type I respiratory failure related with hypoxia. But type II respiratory failure related with hypoxia and hypercapnia)
  - ✓ Pneumonia
  - ✓ Pneumothorax
  - ✓ Pulmonary HTN
- ➢ Respiratory infection
  - ✓ Common cold
  - ✓ Flue
  - ✓ Pneumonia
  - ✓ Acute bronchitis
- ➢ Corpulmonale (Isolated RSHF) and Pulmonary HTN
- ➢ Secondary polycythaemia
- ➢ MI
- ➢ Lung ca
- ➢ Depression→ dyspnea prevent patient from doing enjoyfull activities which lead to depression

Sample history

Sample history of a patient from sanja woreda with the DX of cor pulmonale 2ry to COPD

Chief compliant
Exacerbation of SOB of 01-week duration

HPI

For the past 20 years, this patient had a progressively increasing intermittent productive cough with non-foul-smelling, non-blood tinged, sputum of 3-4 Arabic coffee cup per day which later became increased up-to 10 Arabic coffee cup/day which is aggravated by dust and increase in intensity and frequency at night.

Four years back she was having insidious onset of progressively increasing shortness of breath. For this she visited sanja primary hospital where she was admitted and told to have lung disease (unspecified) after CXR and blood examination was done and she was on intra nasal oxygen and discharged after 2 weeks of hospital stay. For the same compliant she had a total of 4 admissions.

Two weeks prior to her admission, she started to experience generalized body swelling which starts from foot and goes upwards to involve the leg, abdomen and finally the face associated with stabbing type of RUQ abdominal pain, loss of appetite and Unquantified but significant weight loss to the extent her closes become loose but no Orthopnea, PND, chest pain or palpitation.

Currently presented with exacerbation of shortness of breath while doing supra ordinary activities like fetching water from long distance which later worsen to the extent of dyspnea at rest.

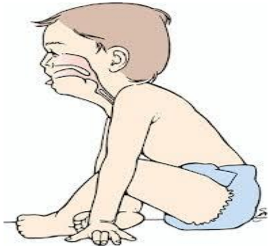
- *She cooks 3x/day in muddy kitchen which has no windows. And she has dust exposure throughout her life while cleaning the house and excreta of cattle's.* She is and lives in a family size of 6. all are alive and healthy, they live in iron corrugated house having 2 rooms, one windows and one door (all are functional.), they have separate kitchen and toilet room *(indoor air pollution)*
- Her husband is a farmer, she is house wife, Claimed that, their income is enough to support the family/if possible, quantify/ *(socioeconomic status is RF, to assess Work place dust exposure, such as factory workers, coal mining, cotton textile industry)*
- She experienced cough, rhinorrhea, fever and sore throat repeatedly where she was treated at a local health center multiple times. *(URTI are RF for exacerbation of COPD or may happen as a complication of COPD)*
- No hx of cigarette smoking or hemoptysis *(smoking is RF for both COPD, Emphysema and Lung ca → the last is DDX or CXN)*
- No family hx of similar illness *(genetic→ AAT deficiency)*
- He/she usually eats injera made of "teff" and "machilla" and "wott" made of "atter" and "dagusa" 3-4 times per day. Occasionally he/she eats meat during holidays *(nutrition)*
- No hx of contact with a known TB patient or previous TB treatment *(post TB fibrosis as DDX)*
- No self or family hx of DM, HTN or Asthma *(RF and DDX)*
- Screened for RVI 6 months back and found to be NR *(RF)*
- No hx of bone pain, herbicide exposure, epistaxis or bleeding from other body sites *(mediastinal lymphoma → DDX)*
- No hx of drug intake other than those mentioned above *(drugs as a cause of cough e.g. amiodarone, methotrexate, hydralazine, ACE-I)*

Finally, S/he was admitted to our hospital supported physically by his families

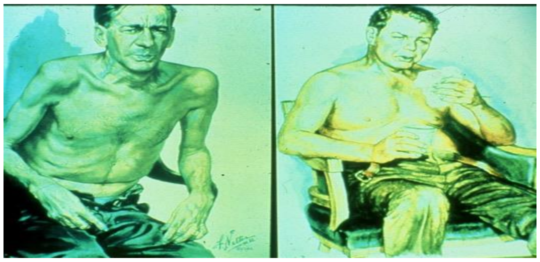
Physical examination (pertinent findings)

1. GA

- Respiratory distress signs (e.g. use of accessory muscle of Respiration)
- "tripod" position



Picture; "***tripod position***"; child is **sitting up and leaning forward** on outstretched hands, **to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles** which helps to decrease respiratory distress (RD). This is a patient with epiglottitis who developed RD, we put here to have Knowhow of tripod position



Picture; **Left) "Tripod position"** in patient with emphysema, Right) Patient with Chronic bronchitis sitting comfortably. But this is not necessarily the Stereotype (the opposite form may be seen).

- Low BMI, with significant weight loss → Due to inadequate oral intake
- Previously the consideration was; Pink puffers (emphysema) tilt forward, blue bloaters (chronic bronchitis) sit comfortably
    - Nowadays, classifying patients as Pink puffers and blue bloaters is obsolete, because most patients have features of both chronic bronchitis and emphysema

2. **Vital signs**
    - ✓ Febrile → if there is acute respiratory infection
    - ✓ Desaturated patient (decreased O2 saturation)
3. **HEENT**
    - ✓ Plethora (injected and hyperemic conjunctiva) → 2ry to polycythemia
    - ✓ Anemia features → pale conjunctiva
    - ✓ Central cyanosis
4. **LGS**

5. **RS**
    - ✓ **Inspection**
        - Use of accessory muscles of respiration → predominantly in emphysema
        - Pursing of lips → close lips tightly during expiration (in emphysema)
        - Reduced tracheal length above the sternal notch
        - Tracheal tug → trachea descend during inspiration
        - Subcostal and intercostal retraction
        - Jugular vein distension during expiration
        - Barrel shaped chest → AP diameter of chest > lateral diameter due to hyperinflation → cmn in emphysema
        - Central cyanosis → predominantly in chronic bronchitis
        - Hoover's sign +ve → paradoxical inward movement of ribcage with inspiration
    - ✓ **Palpation**
        - Decreased chest expansion bilaterally → like restrictive lung disease
        - Tracheal tug
    - ✓ **Percussion**
        - hyper resonant → cmn in emphysema
        - loss of cardiac and liver dullness → flattening of diaphragm
        - poor diaphragmatic excursion → enlarged liver volume
    - ✓ **auscultation**
        - decreased Air entry bilaterally
        - vesicular breath sound with prolonged expiration

  - coarse crepitation (crackles) and wheeze at lung bases throughout the respiratory cycle
  - Ronchi at expiration

N.B type II respiratory failure features

- Central cyanosis
- Flapping tremor
- Bounding pulse
- CHF features (raised JVP, right ventricular heave, loud P2, hepatomegaly, pedal edema)

6. **CVS**
   - ✓ Distended neck vein from RSHF → N.B. Neck vein distension, liver enlargement and peripheral oedema could be due to cor pulmonale or due to severe hyperinflation.
   - ✓ Parasternal heave from RV hypertrophy in pulmonary HTN
   - ✓ Split of S2 which suggests corpulmonale
   - ✓ Murmur of TR and PR
   - ✓ Distant heart sound
7. **Abdominal examination**
   - ✓ Easily palpable liver due to severe hyperinflation or due to congestion from RSHF.
     - In the case of RSHF it is tender hepatomegaly. In severe hyperinflation, liver may palpable due to pushing down effect from diaphragm but, it doesn't mean hepatomegaly. SO, Hepatomegaly is after measuring TVLS.

8 GUS

9 MSS

- ✓ Peripheral edema from cor pulmonale
- ✓ Loss of muscle mass and peripheral muscle weakness are consistent with malnutrition and /or skeletal muscle dysfunction.

10 IS

- ✓ cyanosis

11 NS

Signs of Cor pulmonale can be summarized as the follows (Source → Harrison 20th edition)

Physical examination findings of Cor pulmonale include;

- Findings of **pulmonary hypertension** such as
  - **Accentuated P2** component of S2
  - **A right-sided S3 or S4, and TR.**
- Auscultation of the lungs can highlight the **underlying parenchymal lung disorder**
- In chronic cor pulmonale, the murmur of **TR**, an **S3 gallop** and a **RV heave** palpable along the left sternal border

- **The most blatant findings** are reflective of high right-sided filling pressures and hypervolemia such as
  - **Elevated JVP**
  - **Hepatomegaly**
  - **Pulsatile liver**
  - **Ascites, and especially lower-extremity edema.**
- **Cyanosis** is a late finding in cor pulmonale

Signs of COPD can be summarized as the follows (Source → Harrison 20th edition)

- **In the early stages** of COPD, patients usually have an **entirely normal** physical examination.
- Current smokers may have signs of active smoking, including;
  - **An odor of smoke** or
  - **Nicotine staining of fingernails**.
- **Expiratory wheezing** → In patients with more severe disease
- **A barrel chest** and **enlarged lung volumes with poor diaphragmatic excursion** → signs of hyperinflation
- Patients with severe airflow obstruction may also exhibit;
  - **Use of accessory muscles of respiration**
  - Sitting in the characteristic **"tripod" position** → to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles.
- **Cyanosis,** visible in the lips and nail beds.
- **Cachexia, with significant weight loss**, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue → may happen in Advanced disease
  - **Associated with** both **inadequate oral intake** and elevated levels of inflammatory cytokines (TNF-α).
  - **An independent poor prognostic factor in COPD**.
- **Hoover's sign** (Paradoxical inward movement of the rib cage with inspiration)
  - Seen In advanced disease
  - The result of alteration of the vector of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation.
- **Signs of overt right heart failure, termed *Cor pulmonale*, are relatively infrequent** since the advent of supplemental oxygen therapy.
- **Clubbing of the digits is not a sign of COPD**
  - Its presence should alert the clinician to initiate an investigation for causes of clubbing (the development of **lung cancer is the most likely explanation for newly developed clubbing**).
- *Although **traditional teaching** is that patients with predominant emphysema, termed "pink puffers," are thin and noncyanotic at rest and have prominent use of accessory muscles, and patients with chronic bronchitis are more likely to be heavy and cyanotic ("blue bloaters"), **current evidence demonstrates that** most patients have elements of both chronic bronchitis and emphysema **and that the physical examination does not reliably differentiate the two entities.***

DDX

Differential diagnosis of COPD

- **Suggestive Features for differentiation**, we put here, tend to be **characteristic of the respective diseases, but do not occur in every case.**
  - For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

1) **COPD**
   - Onset in mid-life; onset in early adulthood should prompt suspicion for alpha-1 antitrypsin deficiency
   - Symptoms slowly progressive
   - Long smoking history, although can occur in nonsmokers
   - Dyspnea during exercise
   - Largely irreversible airflow limitation
2) **Asthma**
   - i.e. Severe and severe persistent form of asthma are DDX for COPD
   - It may be one of the variants of COPD
   - seasonal and there may be triggering agents
   - Symptoms vary from day to day, more at night/early morning
   - wheezing is predominant
   - Onset early in life (common in childhood, peak at 3 years)
   - Allergy, rhinitis, and/or eczema also present
   - +ve Family history of asthma
   - Largely reversible airflow limitation
3) **Bronchiectasis**
   - Cough and large volume of mucopurulent, tenacious, position dependent, sputum last for months to years
   - There may be hemoptysis
   - Commonly associated with recurrent or persistent bacterial infection
   - Coarse crackles on auscultation, clubbing of digits
   - Chest radiograph/HRCT shows bronchial dilation, bronchial wall thickening
   - ''Trump truck sign'' and ''signet ring sign'' in high resolution CT (HRCT) → continuous non tapering airway with bronchial dilatation and bronchial wall thickening
     - N.B HRCT is gold standard Ix for bronchiectasis
   - Obstructive spirometry finding
   - Bronchiectasis is 2ry to
     - Acquired → TB (Post TB fibrosis is the commonest cause in our setup), pneumonia, obstruction of the bronchial tree

- Congenital → Cystic Fibrosis (common in westerns)

4) **Tuberculosis**
   - Typical features of TB (Cough more than 2 weeks associated with Fever weight loss, night seat)
   - Maye have contact history
   - Onset all ages
   - Chest radiograph shows upper lung zone scarring and/or calcified granulomata
   - High local prevalence of tuberculosis especially in developing countries
5) **Heart failure**
   - Fine basilar crackles on auscultation
   - Dyspnea associated with Orthopnea, PND and Signs of Congestion if there is CHF
   - Chest radiograph shows dilated heart, pulmonary edema
6) **Lung ca**
   - Primary lung ca or metastasis from breast, bowel, bladder, brain….
   - Present with bloody sputum and chronic cough
   - Patients have family hx lung ca and cmn in smokers
   - N.B. the pneumonic **"S" with smoking** in lung ca

Smoking and central	Non-smokers and peripheral
❖ SCC ❖ Small cell carcinoma ❖ SOB and cough are common presentation	❖ Adenocarcinoma ❖ Large cell carcinoma ❖ Hemoptysis and chest pain are common presentations

7) Central airway obstruction (e.g. Bronchogenic or metastatic cancer, lymphadenopathy, Mediastinal mass, scarring from endotracheal tube)
   - Monophonic wheeze or stridor
   - Chest radiograph often normal
   - Airway narrowing on three-dimensional reconstruction of HRCT scan
   - Variable inspiratory or fixed slowing on flow volume loop
   - May end up with superior vanacava sxx

N.B 4T's of mediastinal mass

- Terrible lymphoma (NHL is cmn)
- Thyroid mass (retrosternal extension of thyroid mass)
- Teratoma
- Thymoma

8) Drugs
   - E.g. amiodarone, methotrexate, hydralazine, ACE-I…
   - Result in pulmonary fibrosis
   - Smx resolve if the drug is discontinued
   - End up with irreversible sxx, if there is chronic exposure
9) Porto systemic schistosomiasis
10) OSA (Obstructive sleep apnea)/ untreated/
    - Snoring at night, daytime somnolence
    - Common in obese and DM pt's

11) Obliterative bronchiolitis
  - Rare
  - Onset in younger age, nonsmokers
  - May have history of rheumatoid arthritis or fume exposure
  - HRCT on expiration shows hypodense areas, mosaic pattern

12) Diffuse pan bronchiolitis
  - Extremely rare to consider in our setup, Highest prevalence in East Asia
  - Most patients are male and nonsmokers
  - Almost all have chronic sinusitis
  - Chest radiograph and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

DDX for COPD exacerbations

- Pneumonia
- Pneumothorax
- Pulmonary embolus (PE) → should also be considered, as the incidence of PE is increased in COPD exacerbations.
- Pulmonary edema (Cardiogenic)
- Pleural effusion
- Cardiac Arrythmias (Atrial fibrillation/flutter)

DDX for Cor pulmonale

- CHF
- Constrictive pericarditis
- RCMP (Restrictive cardiomyopathy)
- Right ventricular infarction
- Atrial myxoma
- VSD (Ventricular septal defect)

Table; Aetiology of Chronic Cor Pulmonale (i.e Cor pulmonale 2ry to;)

1. Diseases of the Lung Parenchyma

- **COPD**
  - **Although COPD is responsible for ~50% of the cases of Cor pulmonale** *(western data),* **any disease that affects the pulmonary vasculature or parenchyma can lead to Cor pulmonale.**
  - **Common Variants of COPD include**
    - Chronic bronchitis
    - Emphysema
- **Bronchiectasis**
- **Post TB fibrosis**
  - **Common in developing countries (common cause of Cor pulmonale in our setup. No specific data in Ethiopia to compare with COPD,** but it is known that, Post TB fibrosis is the commonest cause of Bronchiectasis in Ethiopia**)**
  - Most patients have hx of TB treatment with cure and relapse multiple times

- ILD
  - **Pt's present with prolonged unexplained SOB, dry cough**
  - Classified as
    - Known/idiopathic
    - Acute/subacute/chronic
    - Granulomatous/inflammatory
  - **There are so many disorders (>200) which classified under ILD** because they have similar C/F, radiologic feature and mgt. such as;
    - Idiopathic interstitial pneumonias (**idiopathic pulmonary fibrosis/IPF/**)
      - **IPF is the commonest form of ILD**
    - Secondary interstitial diseases
    - Sarcoidosis
- Combined pulmonary fibrosis and emphysema
- Others including Developmental lung disorders (e.g. Bronchopulmonary dysplasia in infants)

2. Disorders of Chronic (Alveolar) Hypoxia

- Chest wall disorders
  - **Kyphoscoliosis**
- **Chronic exposure to high altitude**
- Neuromuscular respiratory failure
- Alveolar hypoventilation syndromes
- Central hypoventilation syndrome

3. Diseases of the Pulmonary Vasculature

- **Pulmonary arterial hypertension (PAH)**
- Chronic thromboembolic pulmonary hypertension (e.g. **Massive PTE in acute cases or Chronic PTE)**
- **Mediastinal disorders affecting central pulmonary vasculature**
- Pulmonary tumour thrombotic microangiopathy

IX

Baseline IX

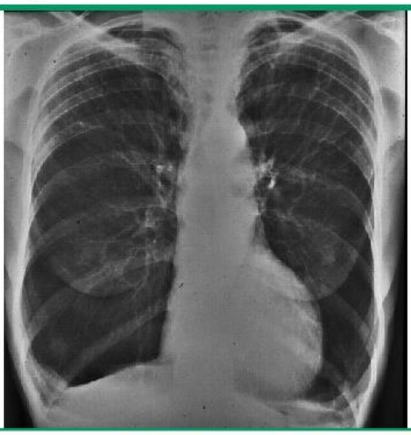
1) **CXR**

Radiographic features suggestive of COPD (usually seen in advanced disease) include:

- ✓ Signs of hyper inflation
  - A flat diaphragmatic contour and an increased retrosternal airspace on a lateral radiograph i.e. Increased A-P Diameter (increased lung volume) which is evidenced by more horizontal alignment of ribs (image 2).
  - Tear drop appearance of heart (narrow vertical heart)
  - Loss of peripheral vascular marking

- ✓ Rapidly tapering vascular shadows, increased radiolucency of the lung, a flat diaphragm, and a long, narrow heart shadow on a frontal radiograph (image 1).
- ✓ Bullae, defined as radiolucent areas > 1cm in diameter and surrounded by arcuate hairline shadows.
  - o They are due to locally severe disease, and may or may not be accompanied by widespread emphysema (image 3).
- ✓ When advanced COPD leads to **pulmonary hypertension and Cor pulmonale;**
  - o Prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space may be seen.
  - o The cardiac enlargement may become evident only by comparison with previous chest radiographs
  - o RV hypertrophy, right atrial dilatation, prominent pulmonary artery
- ✓ CXR also done to r/o pneumonia, lung ca, CHF, pleural effusion from RSHF, and pneumothorax

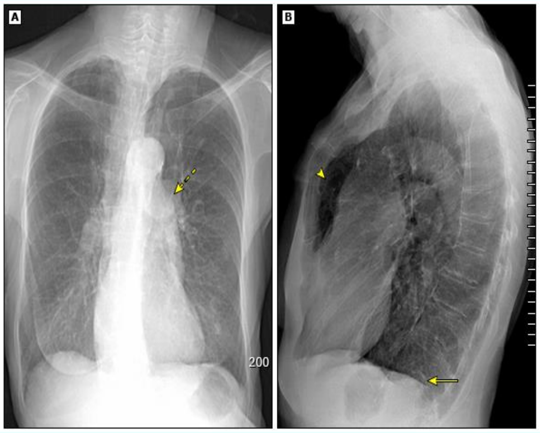
Panacinar emphysema in alpha-1 antitrypsin deficiency



Chest radiograph shows marked hyperexpansion with paucity of vascular strucures at the bases and redistribution of vascular flow to the lesser involved upper lobes. These findings are typical of severe panacinar emphysema.

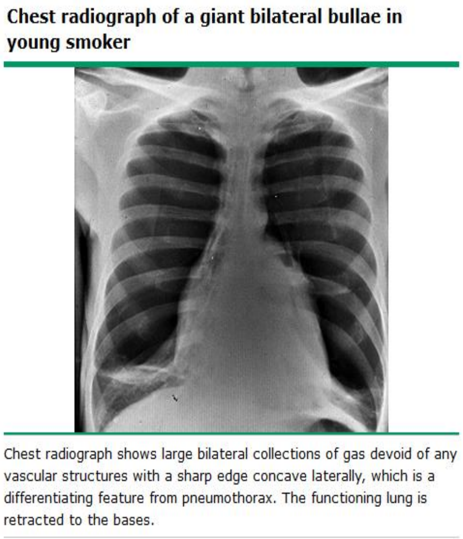
image 1

Chest x-ray emphysema



The posteroanterior (A) and lateral (B) chest x-rays of a 71-year-old female with emphysema show increased lung volumes with flattened hemidiaphragms on the lateral examination (arrow) and increase in the retrosternal space (arrowhead). The normal retrosternal airspace is less than 2.5 cm. A prominent pulmonary artery on the posteroanterior view (dashed arrow) reflects secondary pulmonary hypertension.

image 2



Chest radiograph of a giant bilateral bullae in young smoker

Chest radiograph shows large bilateral collections of gas devoid of any vascular structures with a sharp edge concave laterally, which is a differentiating feature from pneumothorax. The functioning lung is retracted to the bases.

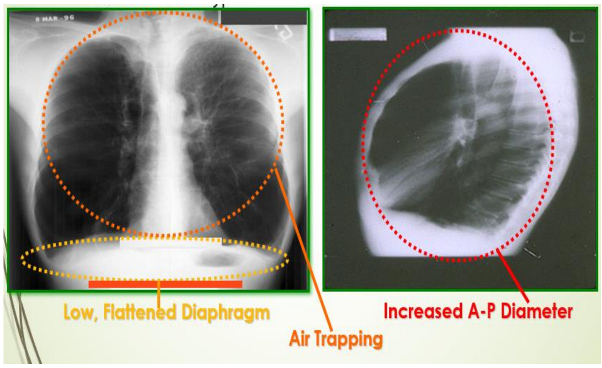


image 3 image 4

CXR **features of Pulmonary hypertension** include;

- **Enlargement of the central pulmonary arteries**, **“vascular pruning,”** and **cardiomegaly**
  - *The term “vascular pruning,” is used to indicate* ***attenuated peripheral pulmonary arteries that looks like a ‘’pruned tree’’***

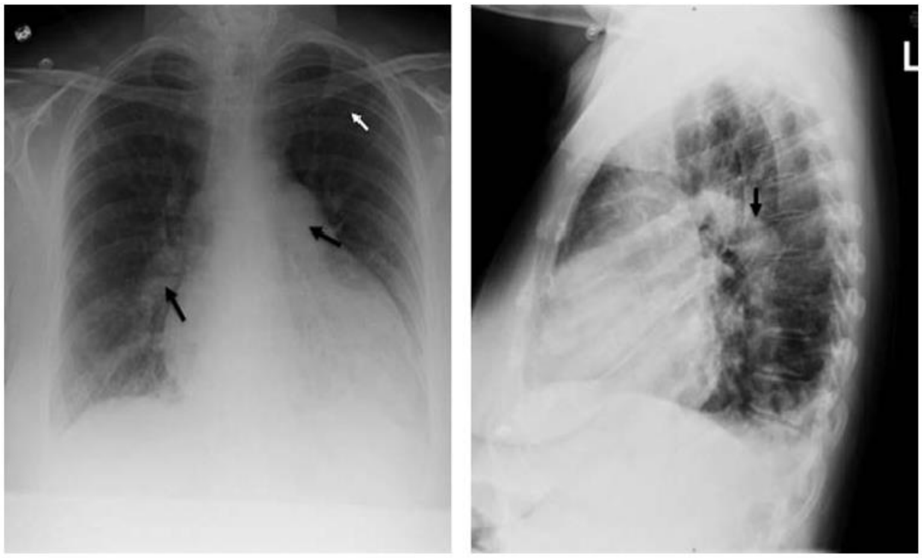
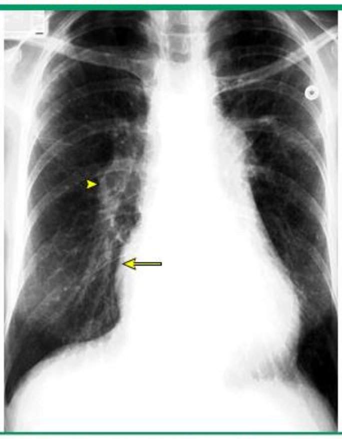


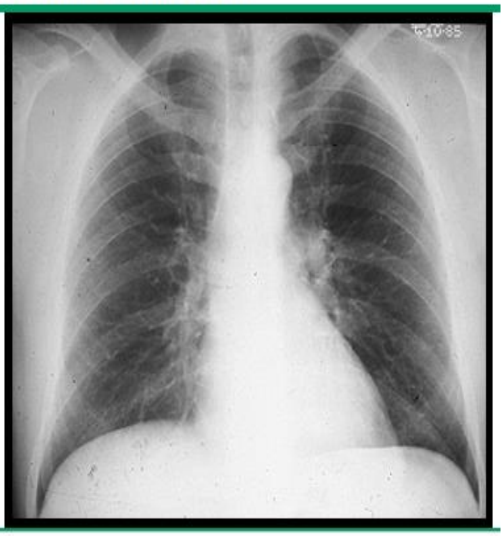
FIGURE 277-3 Postero-anterior (*left*) and lateral (*right*) chest radiograph showing enlarged pulmonary arteries (*black arrows*) and pruning of the distal pulmonary vasculature (*white arrows*) commonly seen with advanced pulmonary arterial hypertension.

Pulmonary hypertension



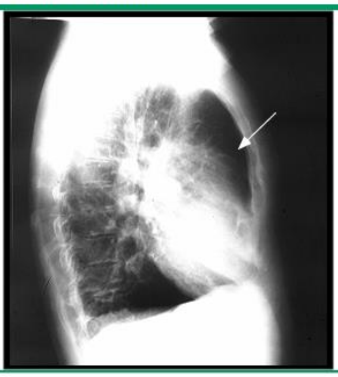
This plain frontal chest radiograph from a 50-year-old male demonstrates prominence of the interstitial pulmonary markings with enlargement of the right and left ventricle and the right atrium (arrow). Additionally, large central, but attenuated peripheral pulmonary arteries are noted (arrowhead), all features characteristic of pulmonary hypertension.

Normal chest radiograph



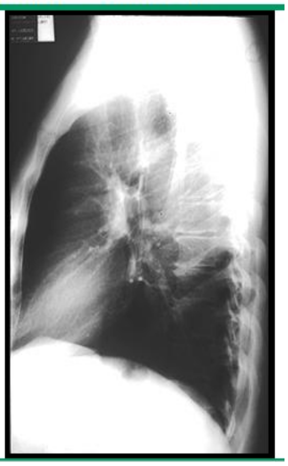
Posteroanterior view of a normal chest radiograph.

Pulmonary hypertension



Chest radiograph in lateral view showing decreased retrosternal space (arrow) due to right ventricular enlargement in pulmonary hypertension.

Normal lateral chest radiograph



2) **ECG** → in Cor pulmonale and Pulmonary hypertension; can show as
   - In severe pulmonary hypertension shows
     - P pulmonale (characteristic peaked P wave)
     - Right axis deviation, and
     - RV hypertrophy (R/S ratio > 1)
   - Supraventricular hypertrophy
   - Dysrhythmia such as Atrial flutter

3) **Echo**
   - Used for the diagnosis of isolated RSHF (Cor pulmonale), Pulmonary HTN and helps to r/o LSHF
   - In Cor pulmonale
     - Echo Used to measure RV wall thickness and chamber dimensions

- The interventricular septum may move paradoxically during systole in the presence of RV pressure overload, highlighting a deleterious interaction between the RV and the LV.

- N.B. MRI is also useful for assessing RV structure and function, particularly in patients who are difficult to image with 2-D echocardiography because of severe lung disease

- Pulmonary hypertension (PH)
  - All forms of PH may demonstrate **a hypertrophied and dilated right ventricle** with **elevated estimated pulmonary artery systolic pressure**
  - Doppler echocardiography can be used to assess pulmonary artery pressures
    - PH can be diagnosed when Pulmonary artery pressure greater than 25mmhg (after Right heart catheterization)
    - Cardiac catheterization (in western setups, not applicable in our setup) → confirms the diagnosis of pulmonary hypertension and can exclude elevated left-sided pressures as a cause for right-sided HF
  - Echo is also important **to identify etiologies of PH**, such as;
    - Valvular disease
    - Left ventricular systolic and diastolic dysfunction
    - Intracardiac shunts, and other cardiac diseases.
  - TR (functional murmur) can be detected either by physical examination or Echo

4) **CBC** → what do you expect from CBC
   - ✓ Polycythemia commonly
   - ✓ Anemia
   - ✓ Leukocytosis as evidence of infection
   - ✓ 2ry erythrocytosis
5) **Sputum examination (BAL)**→ In acute exacerbation it reveals TB, pneumonia
6) **PICT, RBS, LFT and RFT** *(OFT is based on indication)* → to asses comorbidity

Other Ix to be done if available

7) **Diagnostic investigations for COPD**
   PFT /Pulmonary function test/(Spirometry)
   - ✓ Spirometry is “the gold standard”, most reproducible, standardized, objective way of measuring airflow limitation
   - ✓ Expiratory airflow limitation is the hallmark physiologic change of COPD → FEV_1, FVC, FEV_1/FVC all decreased
   - ✓ A postbronchodilator FEV1/FVC ratio < 70% i.e. < 0.7, in combination with an FEV1 < 80% predicted (**obstructive pattern**)
     - ✓ In an individual with cough, sputum production or dyspnea and exposure to risk factors confirms the diagnosis

- Bronchodilator reversibility should be performed at least once to exclude asthma and to establish the best lung function for the individual patient, and, to a lesser degree, to estimate the prognosis.
  - N.B. in COPD, obstruction not improved with short acting bronchodilator administration but in bronchial asthma there will be > 12 % improvement of FEV1 after 15 min administration of short acting bronchodilator (like salbutamol)
- **Other diagnostic tests**
  - Sample of sputum
  - Chest X-ray
  - High resolution CT (HRCT)
  - Arterial blood gases
  - Pulse Oximeter → it is part of physical examination but very necessary for diagnosis
- *Look at GOLD staging of COPD based on Spirometry and clinical parameters under discussion part of COPD below*

How can we differentiate obstructive lung disease (e.g. COPD, Asthma) from Restrictive lung disease (e.g. ILD) based on spirometry?

- **In obstructive lung disease,** FEV1 decreased but FVC is normal so FEV1/FVC **ratio decreased**. In **restrictive lung disease**, FEV1 and FVC decreased simultaneously so the FEV1/FVC **ratio is normal**.

8) HRCT (High resolution CT)

- **CT scanning is not needed for the routine diagnosis of COPD**. Usually, it is performed when;
  - A change in symptoms suggests a complication of COPD (eg, pneumonia, pneumothorax, giant bullae)
  - An alternate diagnosis (eg, thromboembolic disease), or
  - A patient is being considered for lung volume reduction surgery or lung transplantation
- CT Assist in classification of COPD. It has **high sensitivity and specificity than CXR for emphysema**
  - Certain CT scan features can determine whether the emphysema is centriacinar (centrilobular), panacinar, or paraseptal, although this is usually not necessary for clinical management
- Classic findings of Pulmonary Hypertension on CT include;
  - Those found on chest radiograph
  - Enlarged pulmonary arteries, peripheral pruning of the small vessels, and enlarged right ventricle and atrium.
  - However, high-resolution CT may also reveal signs of venous congestion, including centrilobular ground glass infiltrate and thickened septal lines.
  - In the absence of left heart disease, these findings suggest pulmonary venous disease, a rare cause of PAH that can be quite challenging to diagnose.
  - CT is also critical for distinguishing co-morbid interstitial lung disease or emphysema.

- N.B. HRCT is important Ix modality for bronchiectasis, ILD, lung ca, massive PTE, lung abscess

9) **ABG/Arterial blood gas/ analysis** in Cor pulmonale 2ry to chronic lung disorders, typically reveal hypoxemia with or without hypercapnia (decreased PaO_2 and increased $PaCO_2$).
10) **Serum AAT level** → normal range is 100 - 200 mg/dL, low or deficient in emphysema.
11) Thrombophilia screen → to detect chronic venous thromboembolism (proteins C and S, ant thrombin III, homocysteine levels)
12) ANA → SLE Blood culture → for severe pneumonia in RVI pt, has 10 % sensitivity
13) **ADF** → pleural marker
14) BNP → elevated in patients with Cor pulmonale secondary to RV myocardial stretch
15) Lung Biopsy
    - ✓ last option
    - ✓ Biopsy shows emphysema subtypes (centri-acinar, pan-acinar, para-septal, irregular)

Discussion

2.1. Cor pulmonale and Pulmonary Hypertension

- Cor pulmonale is a Latin word meaning ''Pulmonary heart''
- Cor pulmonale is an isolated right sided failure which results from pulmonary hypertension
- Cor pulmonale, also referred to as pulmonary heart disease, is broadly defined by **altered RV/right ventricle/ structure and/or function in the context of chronic lung disease** and is triggered by the presence of pulmonary hypertension.
- On the other way, cor pulmonale can be defined as the enlargement and failure of the right ventricle of the heart as a response to increased vascular resistance (such as from pulmonary stenosis) or high blood pressure in the lungs.
- Although Right Ventricular dysfunction is an important sequela of HFpEF (Heart failure with preserved ejection fraction) and HFrEF (Heart failure with reduced ejection fraction), this is not considered as cor pulmonale. So, **to be classified as pulmonary heart disease, the cause must originate from the lung** (i.e. in the pulmonary circulation system)
- Right ventricular Hypertrophy due to a systemic defect is not classified as pulmonary heart disease. The heart and lungs are intricately related; whenever the heart is affected by a disease, the lungs risk following and vice versa.

Etiology and epidemiology

- Chronic cor pulmonale develops in response to chronic pulmonary hypertension resulting from parenchymal lung disorders, primary pulmonary vascular diseases, or conditions leading to alveolar hypoxia (see table above).
- The true prevalence of cor pulmonale is difficult to ascertain.
    - First, not all patients with chronic lung disease will develop cor pulmonale, which may be subclinical in compensated individuals.
    - Second, the ability to detect pulmonary hypertension and cor pulmonale by routine physical examination and laboratory testing is relatively insensitive
- Once susceptible patients develop cor pulmonale, their prognosis worsens, regardless of the underlying etiology.
- **Although** COPD is responsible for ~50% of the cases of cor pulmonale *(western data),* **any disease that affects the pulmonary vasculature or parenchyma can lead to cor pulmonale.**
- Primary pulmonary vascular disorders, such as pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, are relatively rare causes of cor pulmonale, but cor pulmonale is extremely common with these conditions, given the magnitude of elevated pulmonary artery pressures and pulmonary vascular resistance.
- Look at the table from DDX part of patient approach above

Pathophysiology

- Although many conditions can lead to cor pulmonale, **the common pathophysiologic mechanism is pulmonary hypertension and increased RV afterload sufficient to alter RV structure (i.e., dilation with or without hypertrophy) and function.**
    - **Normally, mean pulmonary artery pressure is only ~15 mmHg** (does not increase significantly even with increasing multiples of cardiac output because of pulmonary vasodilation and blood vessel recruitment in the pulmonary circulatory bed)
- In the setting of parenchymal lung diseases, primary pulmonary vascular disorders, or chronic (alveolar) hypoxia, the circulatory bed undergoes vascular remodeling, vasoconstriction, and destruction. As a result, pulmonary artery pressures and RV afterload increases, setting the stage for cor pulmonale
- The systemic consequences of cor pulmonale relate to alterations in cardiac output as well as salt and water homeostasis.
- Anatomically, the RV is a thin-walled, compliant chamber better suited to handle volume overload than pressure overload. Thus, the sustained pressure overload eventually leads to RV dysfunction and failure.
- **The response of the RV to pulmonary hypertension depends on the acuteness and severity of the pressure overload.**
    - **Acute cor pulmonale** occurs after a sudden and severe stimulus (e.g., massive pulmonary embolus), with RV dilatation and failure but no RV hypertrophy.
    - **Chronic cor pulmonale**, however, evolves slowly and in conjunction with modest, compensatory RV hypertrophy that lowers wall tension and preserves RV function. Over time, RV dilation ensues leading to an increase in RV wall tension and overt dysfunction.

  - **Acute decompensation of compensated chronic cor pulmonale** is a common clinical occurrence.
- **Triggers** include;
  - Worsening hypoxia from any cause (e.g. pneumonia)
  - Acidemia (e.g., exacerbation of COPD)
  - Acute pulmonary embolus
  - Atrial tachyarrhythmia
  - Hypervolemia, and
  - Mechanical ventilation that compresses blood vessels associated with alveoli and further increasing RV afterload.

Clinical features and Investigation → look at the approach section above

Treatment

- **Identification and treatment of the underlying cause is the mainstay of treatment**
- The treatment for cor pulmonale may include the following;
  - **Oxygen therapy**
    - Oxygen is often required to resolve the shortness of breath. Additionally, oxygen to the lungs also helps relax the blood vessels and eases right heart failure.
    - Look at below, indications for home oxygen, under COPD management
  - **Antibiotics** → if there is acute exacerbation or sign of infection
  - **Diuretics** → to decrease strain on the heart;
    - **Diuretics should be used with caution.**
    - In RSHF Hypervolemia is preload dependent, **minimal and moderate dose of diuretics may end up with cardiogenic shock. So, slow and cautious escalation is needed**
    - ACE-inhibitors [with diuretics] used for cardiac remodeling effect
    - But, in LSHF Diuretics can be escalated up easily unless there is low BP from the onset. (e.g. furosemide 20-40 mg IV, double the dose every 2-4hours, max. 400-600mg/day)
  - **Phlebotomy (Venesection)**→ is used **in severe secondary polycythemia** (because of hypoxia), which improves symptoms though survival rate has not been proven to increase.
  - Expectorants
  - Digitalis
  - Bronchodilators → When wheezing is present, the majority of individuals require a bronchodilator.
  - Anticoagulants → are used when venous thromboembolism is present.
  - Transplantation → Finally, transplantation of single/double lung in extreme cases of cor pulmonale is also an option.

Pulmonary hypertension (PH)

- Pulmonary hypertension (PH) is a spectrum of diseases involving the pulmonary vasculature, and defined as an elevation in pulmonary arterial pressures (mean pulmonary artery pressure [PAP] >22 mmHg or an estimated systolic PAP >36 mmHg).
- Pulmonary arterial hypertension (PAH) is a relatively rare form of PH and is characterized by symptoms of dyspnea, chest pain, and syncope.
- If left untreated, the disease carries a high mortality rate, with the most common cause of death being decompensated right heart failure.

Clinical features

- The diagnosis of PH can be missed without a reasonable **high index of suspicion.**
- PH **symptoms are nonspecific**, insidious, and overlap considerably with many common conditions, including asthma and other lung disease, and cardiac disease.
- **Most patients will present with dyspnea and/or fatigue**, whereas **edema, chest pain, presyncope, and syncope are less common** and associated with more advanced disease.
- In early phases of PAH, the physical examination is often unrevealing.
- As the disease progresses there may be **evidence of RSHF** with **elevated JVP, lower extremity edema, and ascites**.
- Additionally, the CVS examination may reveal an **accentuated P2 component of the S_2 (typical sign for PH) a right-sided S3 or S4, and TR**.
- **Clubbing** may be seen in some chronic lung diseases
- **Crackles** on examination of the lungs **and systemic hypertension** may be **clues to left-sided systolic or diastolic heart failure**.

Investigations → see the approach section above

- PFT (Pulmonary function tests)
  - Results of PFT may suggest **restrictive or obstructive lung diseases** as the cause of dyspnea or PH
  - N.B an isolated reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) is the classic finding in PAH,
- LFT, HBsAg → to screen for underlying liver disease
- BNP → Important in diagnosis and management of PH
- RHC (**Right heart catheterization**) with pulmonary vasodilator testing
  - Remains **the gold standard both to establish the diagnosis of PH and to guide selection of Appropriate medical therapy.**
  - The definition of precapillary PH or PAH requires;
    - An increased **mean pulmonary arterial pressure (mPAP >25 mmHg**)
    - A pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg; and
    - Total pulmonary vascular resistance (PVR) >3 Wood units.

Classification system of Pulmonary hypertension

- **WHO classifies patients with PH into five groups based upon etiology.**

- WHO functional classification for pulmonary hypertension (Class I to Class IV) is the same as NYHA functional classification of Heart failure.
  - The only difference is, Patients with pulmonary hypertension in WHO but Patients with cardiac disease in NYHA (click here → Chapter 1; Heart failure (ልብ ድካም))

☛ **Group I; PAH (pulmonary arterial Hypertension)**

- **Relatively rare cause of PH and diagnosis of exclusion**
- PAH includes a group of diseases and defined as a sustained elevation in resting mPAP $\geq$25 mmHg based on Right heart catheterization
- It can be further classified as
  - Idiopathic PAH
  - Heritable
  - Drug- and toxin-induced
  - Associated with Connective tissue diseases, HIV infection, Portal hypertension, Congenital heart diseases, Schistosomiasis

☛ **Group II; PH due to left heart disease**

- **The commonest cause of PH**
- WHO Group II PH includes;
  - Left heart systolic dysfunction
  - Aortic and mitral valve disease, and
  - Heart failure with preserved ejection fraction (HFpEF)
- The hallmark of Group II PH is elevated left atrial pressure with resulting pulmonary venous hypertension
- Increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure.
- The presence of **PH portends a poor prognosis in all forms of heart failure**

☛ Group III; **PH due to chronic lung disease**

- Intrinsic lung disease is the **second most common cause of PH**
- PH has been observed in both **COPD and ILD (from ILD, Commonly in idiopathic pulmonary fibrosis)**
- It can also be seen in diseases with **mixed obstructive/restrictive physiology**: **bronchiectasis, cystic fibrosis**, **emphysema** predominantly in the upper lung zones and mixed obstructive restrictive disease marked by fibrosis in the lower lung zones

☛ Group IV; **PH associated with chronic thromboembolism**

☛ Group V; **PH with unclear multifactorial mechanisms**

- A group of **miscellaneous diseases** that only rarely cause PH, Examples include PH caused by;
  - Hematologic disorders (eg, chronic hemolytic anemia, myeloproliferative disorders, splenectomy)
  - Systemic disorders (eg, sarcoidosis)

  - Metabolic disorders (eg, glycogen storage disease, Gaucher disease, thyroid disorders)
  - Others (e.g. chronic renal failure, tumoral obstruction, fibrosing mediastinitis, segmental pulmonary hypertension)

Management of Pulmonary Hypertension (PH)

- **The baseline severity of PH should be determined prior to the initiation of therapy**
  - **Functional impairment and hemodynamic derangement** are the key determinants of disease severity
  - **The next step is classifying the patient condition based on WHO etiology classification (Group I to V) and WHO functional classification (Class I to IV)**
- **Several therapies should be considered in patients with All groups of PH including diuretic, oxygen, anticoagulant, and digoxin therapy, as well as exercise.**
  - **These therapies should be administered taking into consideration the underlying cause as well as the risks and benefits associated with each therapy.**
- Once the severity of the patient's pulmonary hypertension has been determined, **Treatment of the underlying cause is the mainstay of treatment of PH**

- **Group I → There are no effective primary therapies for most types of group I PAH**. As a result, advanced therapy is often needed
  - Without treatment PAH is invariably fatal.
  - While there is **no cure for PAH**, current pharmacologic therapies improve morbidity, and in some cases, mortality.
  - Management options include;
    - Prostacyclin and prostacyclin analogues and agonists
    - NO (Nitric oxide) pathway enhancers
    - Endothelin receptor antagonists (ERAs) and
    - Combination of those agents
- **Group II →** treatment of the underlying heart disease
- **Group III →** treatment of the underlying cause of hypoxemia and **correction of the hypoxemia with supplemental oxygen.**
  - Oxygen is the only modality with proven mortality benefit in some patients with group III PH
- **Group IV → Anticoagulation** is primary medical therapy for patients with group IV PH
  - **Surgical thromboendarterectomy** is primary surgical therapy **for selected patients** with thromboembolic obstruction of the proximal pulmonary arteries
- **Group V →** treatment of the underlying cause

2.2 Obstructive Lung diseases

2.2.1 COPD (Chronic obstructive pulmonary disease)

- **COPD is defined as a disease state characterized by** persistent respiratory symptoms and airflow limitation that is not fully reversible.
- The classic definition of COPD requires the presence of chronic airflow obstruction, determined by spirometry, that **usually occurs in the setting of noxious environmental exposures–most commonly cigarette smoking. (indoor air pollution in our setup)**

- GOLD[8] (Global Initiative for Chronic Obstructive Lung Disease), defines COPD as:

  "COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."

- COPD includes;
  - ***Emphysema*** → an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement
  - ***Chronic bronchitis*** → a clinically defined condition with chronic cough and phlegm; and
  - ***Small airway disease*** → a condition in which small bronchioles are narrowed and reduced in number.
- Emphysema, chronic bronchitis, and small airway disease are present in varying degrees in different COPD patients.
- Patients with a history of cigarette smoking without chronic airflow obstruction may have chronic bronchitis, emphysema, and dyspnea. Although these patients are not included within the classic definition of COPD, they may have similar disease processes.
- The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person.
- It is **a chronic disease that is showing progressive upward trend in both mortality and morbidity**
- **COPD is the 3rd leading cause of death in the United States.** And also, almost 90% of COPD deaths occur in low- and middle-income countries, where effective strategies for prevention and control are not always implemented or accessible.
- Different guidelines use other forms of terminology for COPD (chronic obstructive pulmonary disease). All of them are the same entities, these are;
  - COLD (chronic obstructive lung disease)

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[8] **2021,** GOLD, COPD diagnosis, management and prevention guideline; Free PDF File download available here → https://www.goldcopd.org

  - COAD (chronic obstructive airway disease)
  - CORD (chronic obstructive Respiratory disease)
- Although COPD affects the lungs, it also produces significant systemic consequences.
- Some patients can have manifestations of both COPD and asthma and, hence, told to have Asthma COPD overlap syndrome (**ACOS**).

Asthma-COPD overlap syndrome (ACOS)

- Although asthma and COPD are distinct syndromes with different clinical presentations and underlying inflammatory mechanisms, **some patients with asthma have features of COPD** (for example, asthmatics who smoke and severe asthmatics with irreversible airflow limitation) and **some patients with COPD have features of asthma** with more reversibility and increased airway and blood eosinophils.
- This may represent the coincidence of two common diseases, or these may be distinct phenotypes.
- ACOS patients tend to have more symptoms and exacerbations. They may benefit from triple therapy with ICS (Inhalational corticosteroids), LABA (long acting $\beta 2$ agonists), and LAMA (long acting muscarinic antagonists e.g. theophylline)

Difference between Obstructive lung disease (e.g. COPD, Asthma) from Restrictive lung disease (e.g. ILD)

Obstructive lung disease (e.g. COPD, Asthma)	Restrictive lung disease (e.g. ILD)
✓ Spirometry reveals Obstructive pattern - **FEV1 decreased but FVC is normal so FEV1/FVC*** **ratio decreased** $i.e.\frac{FEV1\ decreased}{FVC\ normal}$ = **decreased ratio** - Lung volume measurements reveal a normal to increased value of both RV and TLC, so there is an increase in RV/TLC# ratio. ✓ As the name implies there is airway obstruction and patients present with **SOB, Chronic productive cough** (in asthma patients, even though there is obstruction, there may not have cough at all)	✓ Spirometry reveals a restrictive pattern - **FEV1 and FVC decreased simultaneously so the FEV1/FVC ratio is normal.** $i.e.\frac{FEV1\ decreased}{FVC\ decreased}$ = **Normal ratio** - Lung volume measurements reveal a normal to decreased TLC, and an increase in RV/TLC. This increased RV/TLC ratio may reflect the relative decrease in TLC or a real increase in RV (true hyperinflation) ✓ Patients usually present with **prolonged unexplained SOB, dry cough**

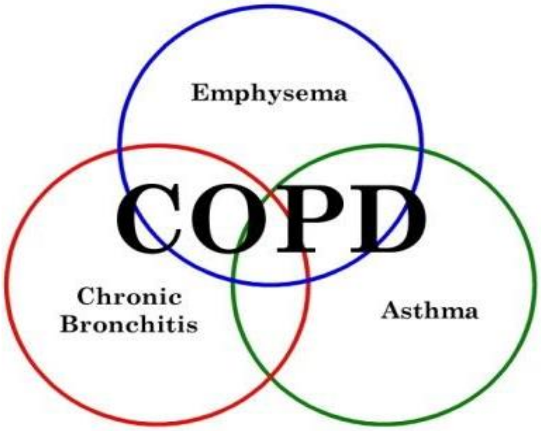
* *FEV1 = Forced expiratory volume in 1 sec, FVC = Forced vital capacity*
# *TLC* = total lung capacity, RV = residual volume

Difference between COPD and Asthma

COPD	ACOS	Asthma*
❖ **Obstruction not improved with short acting bronchodilator**		❖ **There will be > 12 % improvement** (a >12% and 200-mL increase in FEV1),

administration (it may be partially reversible) ❖ ***symptoms show less variability, never completely remit***, and *show much less* (or no) *reversibility to bronchodilators* ❖ COPD *is **more likely in elderly patients** and may coexist with asthma. And **usually have hx of smoking**, in our set up indoor smoking (i.e. **indoor air pollution** from biomass fuel)* ❖ **Slowly progressive** ❖ **Airway remodeling and lung obstruction** ❖ Inflammatory cells ➢ Neutrophilic bronchitis ➢ Eosinophilic during exacerbations	➔ Some patients with asthma cannot be distinguished from COPD with the current diagnostic tests. The management of this patients should be similar to that of asthma ➔ Look at the above notes	**15 min after administration of short acting bronchodilator (like salbutamol),** or in some patients by a 2-4 week trial of oral corticosteroids (OCS) like prednisone or prednisolone 30 - 40 mg daily (may be fully reversible) ❖ **symptoms show variability, seasonal and depends on triggering factors** ❖ **Occur at any age. Especially common in children, peak at 3 years**, 50% develop before the age of 10 and another 35% before 40 ❖ **Episodic course** ❖ **Airway remodelling but no lung obstruction** ➢ **If there is obstruction, the so called Chronic obstructive asthma is subset of COPD** ❖ Inflammatory cells ➢ Eosinophilic bronchitis ➢ Neutrophils in severe disease
* For details of asthma, refer respiratory section from short case on Nitsbin (click here → Asthma (አስም))		

Spectrum of Disease in COPD



COPD Phenotypes include;

- Chronic bronchitis
- **Emphysema:**
- **Chronic obstructive asthma** (Chronic asthma with airway remodeling and fixed obstruction).

Table; difference between Chronic bronchitis and emphysema*

Chronic bronchitis#	**Emphysema**
☛ Chronic bronchitis is defined as **a chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of chronic cough (eg, bronchiectasis) have been excluded.** ➢ **Clinical definition and Dx of exclusion** ☛ Predominant productive cough ➢ Expectoration is due to goblet cell hyperplasia and inflammation ☛ Rhonchi, wheeze and coarse crackles may be heard ☛ It may precede or follow development of airflow limitation. ☛ Symptoms of chronic bronchitis may develop in cigarette smokers as early as 36 years of age and have been associated with a higher frequency of exacerbation events, even in the absence of airflow obstruction.	☛ **An abnormal permanent enlargement of the distal air spaces, distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious (macroscopic) fibrosis.** ➢ **Pathologic definition** ☛ Predominant SOB with little/no cough or expectoration ➢ SOB is due to destruction of gas exchange air spaces which intern forms non-functioning wide Air sac ➢ Production of protease from smoking leads to destruction of basement membrane and connective tissue which will cause emphysema ☛ Use of accessory muscles of respiration and Pursing of lips are predominant in emphysema ☛ Barrel shaped chest with hyperinflated lung that push the diaphragm down (flattening of diaphragm) is common in emphysema

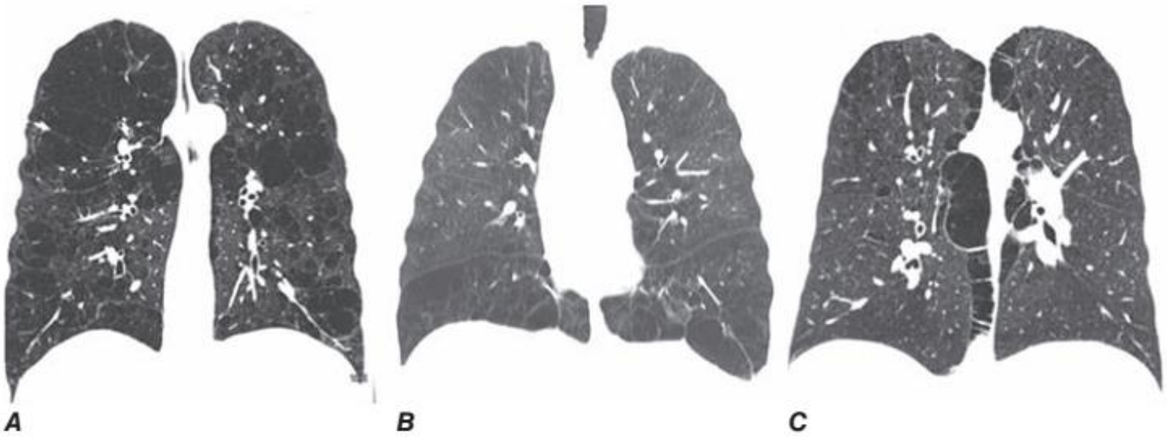
* The old classification of Chronic bronchitis as **"blue bloaters"** and emphysema as **"pink puffers"** is obsolete nowadays.

# **Acute bronchitis** patients present with sore throat, fatigue, fever, runny nose, vomiting and diarrhoea, cough, SOB. While, **Chronic bronchitis** patients present with cough, sputum, cyanosis, hypercapnia, pulmonary hypertension, Right ventricular failure, peripheral edema

Emphysema classification

- Emphysema is classified into distinct pathologic types (Figure below), which include;
  - **Centrilobular** emphysema
  - **Pan lobular** emphysema and
  - **Para septal** emphysema.
- Centrilobular emphysema
  - The type which is most frequently associated with **cigarette smoking**, and characterized by enlarged air spaces **found (initially) in association with respiratory bronchioles.**
  - It is usually most prominent in the **upper lobes and superior segments of lower lobes** and is often quite focal.
- Pan lobular emphysema
  - refers to abnormally large air spaces **evenly distributed within and across acinar units.**
  - It is commonly observed in patients with **α1AT deficiency**, which has a **predilection for the lower lobes**.
- Para septal emphysema
  - occurs in 10 -15% of cases and is **distributed along the pleural margins** with relative sparing of the lung core or central regions.

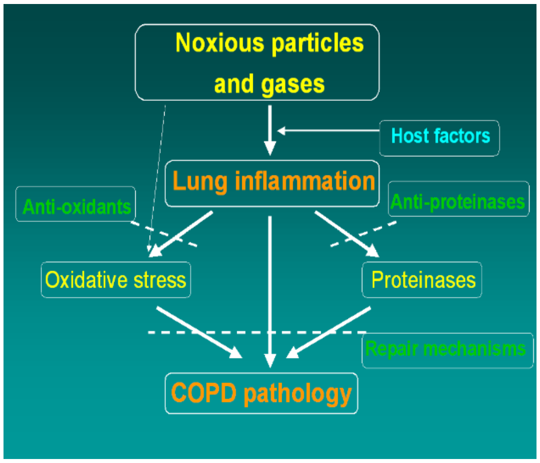
- It is commonly associated with **significant airway inflammation** and with centrilobular emphysema.



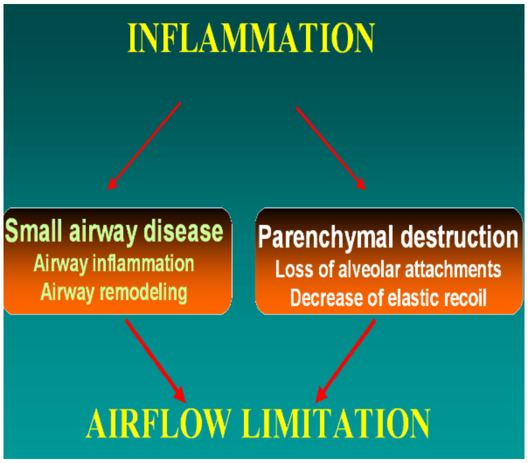
FIGURE; **CT patterns of emphysema**.

A. **Centrilobular emphysema** with severe upper lobe involvement in a 68-year-old man with a 70 pack-year smoking history but forced expiratory volume (FEV1) 81% predicted (GOLD spirometry grade 1)
B. **Pan lobular emphysema** with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α1AT deficiency; and
C. **Para septal emphysema** with marked airway inflammation in a 52-year-old woman with a 37 pack-year smoking history and FEV1 40% predicted.

Pathophysiology



Noxious particles and gases
Host factors
Lung inflammation
Anti-oxidants
Anti-proteinases
Oxidative stress
Proteinases
Repair mechanisms
COPD pathology



INFLAMMATION
Small airway disease
Airway inflammation
Airway remodeling
Parenchymal destruction
Loss of alveolar attachments
Decrease of elastic recoil
AIRFLOW LIMITATION

Causes of Airflow Limitation

Irreversible

- Fibrosis and narrowing of the airways
- Loss of elastic recoil due to alveolar destruction

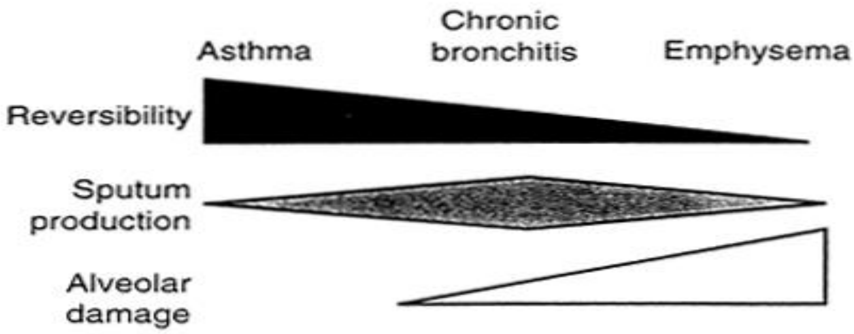
- Destruction of alveolar support that maintains patency of small airways

Reversible

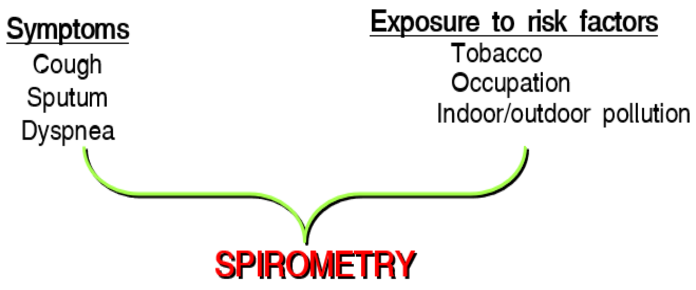
- Accumulation of inflammatory cells, mucus, and plasma exudate in bronchi
- Smooth muscle contraction in peripheral and central airways
- Dynamic hyperinflation during exercise

Natural history

- An accelerated decline in lung function is the single most important feature of COPD.
- COPD is generally a progressive disease, especially if the patient's exposure to noxious substances, most often tobacco smoking, continues.
- If exposure is stopped, the disease may still progress, mainly due to the decline in lung function that normally occurs with ageing.
- Nevertheless, stopping exposure to noxious agents, even after significant airflow limitation is present, can result in some improvement in function and will slow or even hold the progression of the disease.


Asthma
Chronic bronchitis
Emphysema
Reversibility
Sputum production
Alveolar damage

Diagnosis of COPD


Symptoms
Cough
Sputum
Dyspnea
Exposure to risk factors
Tobacco
Occupation
Indoor/outdoor pollution
SPIROMETRY

Presumptive Diagnosis

- COPD should be considered in any patient who has:

- A smoking history of at least 10-20 pack/yrs and/or a history of exposure to other risk factors
- Chronic cough with or without sputum production
- Dyspnea
- Onset of respiratory symptoms in 40s
- Respiratory infection that persists or recurs

For details of Clinical features and Investigation → look at the approach part above

Classification of Severity of Airflow Limitation in COPD

Table; GOLD* Criteria for Severity of Airflow Obstruction in COPD

GOLD stage	Severity	FEV_1 (In patients with FEV_1/FVC ratio < 0.7)
I	Mild	≥ 80% predicted
II	Moderate	FEV1 ≥50% but <80% predicted [50 - 80%)
III	Severe	FEV1 ≥30% but <50% predicted [30 - 50%)
IV	Very severe	FEV_1 < 30% predicted

* GOLD stands for Global Initiative for chronic obstructive lung disease; GOLD guidelines (http://www.goldcopd.org). This table taken from Harrison 20th edition

How can we asses symptom severity of GOLD classification

- Symptom severity is assessed using the CAT score or mMRC grade (CAT = COPD Assessment Tool, mMRC = Modified Medical Research Council)
- Lung function, in addition to the number of exacerbations and hospitalizations for exacerbations in the previous 12 months, can be used to predict future risk.
  - A history of **0 or 1 exacerbation** in the past 12 months **and GOLD I or II** spirometry level suggests a **low future risk of exacerbations**
  - **≥ 2 exacerbations** or a **hospitalized exacerbation** or **GOLD III or IV** spirometry level suggest **a high future risk.**
- These components are combined into four groups as shown the table:

Table; GOLD: COPD severity assessment

Annual frequency of COPD exacerbations/hospitalizations	Respiratory symptoms (based on the mMRC* or CAT# scales)	
	mMRC grade 0 to 1; CAT score <10 **(less symptoms)**	mMRC grade ≥2; CAT sore ≥10 **(High symptoms)**
0 or 1 exacerbations per year without hospitalization **(low risk)**	Group A	Group B
≥2 exacerbations per year or ≥1 hospitalization **(high risk)**	Group C	Group D

***mMRC:** modified Medical Research Council dyspnea scale → Provides a single number for degree of breathlessness:

- 0 → only with strenuous activity
- 1 → hurrying on level ground or walking up a slight hill
- 2 → walk slower than peers or stop walking at their own pace
- 3 → walking about 100 yards or after a few minutes on level ground
- 4 → too breathless to leave the house or when dressing

#**CAT:** COPD Assessment Test → http://www.catestonline.org , *http://www.goldcopd.org*

- An 8-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea on one flight of stairs, limitation in home activities, confidence in leaving the house, sleep and energy.
- Range of total score is 0 - 40.

Management of stable COPD

- The two main goals of therapy are;
  a. To provide **symptomatic relief** → reduce respiratory symptoms, improve exercise tolerance, improve health status and
  b. To **reduce future risk** → prevent disease progression, prevent and treat exacerbations, and reduce mortality.
- The overall approach to managing stable COPD should be characterized by a stepwise increase in the treatment, depending on the severity of the disease.
- **Management principles of COPD include;**
  - **Assessing and monitoring of the disease**
  - **Avoidance of modifiable risk factors and vaccinations**
  - **Oxygen therapy**
  - **Pulmonary rehabilitation.**
  - **Pharmacologic therapies**
  - **Identify and treat complications**
    - Cor pulmonale and RSHF mgt
    - Polycythemia mgt (e.g. phlebotomy)
  - **Surgical management for selected patients**
    - Lung Volume Reduction Surgery
    - Lung Transplantation

A. Assessing and monitoring of the disease

- Factors Determining Severity of Chronic COPD
  - Severity of symptoms
  - Severity of airflow limitation
  - Frequency and severity of exacerbations
  - Presence of complications of COPD, respiratory insufficiency or Comorbidity
  - General health status
  - Number of medications needed to manage the disease.

B. Avoidance of modifiable risk factors and vaccinations

- **Smoking cessation** is the single most effective - and cost effective - intervention to reduce the risk of developing COPD and stop its progression.
  - Brief tobacco dependence treatment (e.g. nicotine replacement) & counseling are effective.
- **Reduction of indoor air pollution** through introduction of non-smoking cooking devices or alternative fuels should be encouraged.
- **Vaccination**
  - **Influenza vaccination** reduces serious illness and death. All Patients with COPD should receive the influenza vaccine **annually.**
  - **Pneumococcal vaccination** (PCV13 and PPSV23): recommended for all patients ≥65. The PPSV23 is also recommended in younger patients with significant comorbidity including chronic lung or heart diseases.

C. Oxygen therapy:

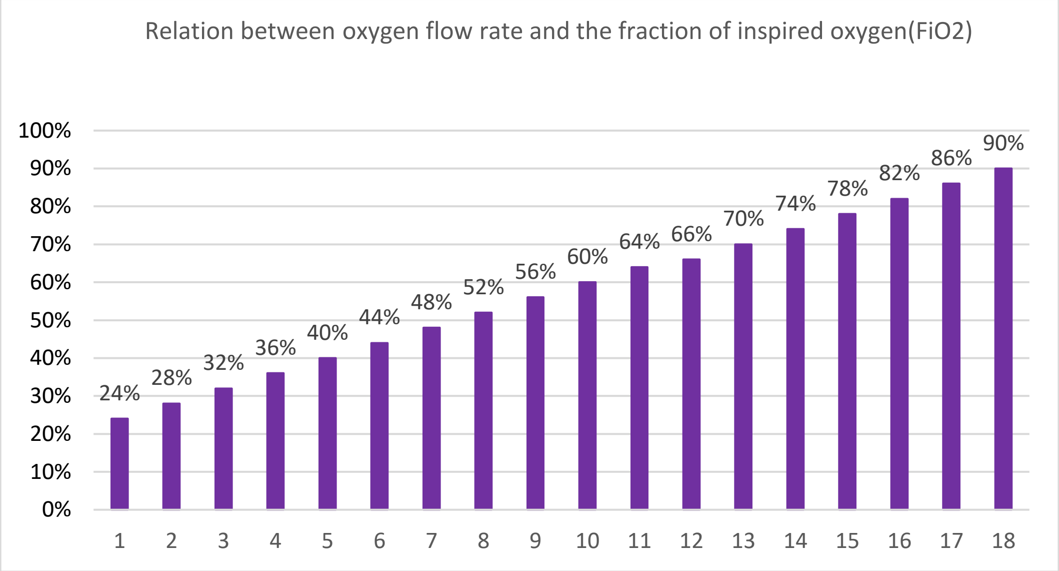
- All patients **with desaturation** should be put on intranasal O_2 during hospital stay.
- In our setup, most patients need home O_2 (so, discharge with O_2, if they can afford, communicate and link to oxygen supply companies)
- Long-term oxygen therapy (LTOT) i.e. **long-term administration of oxygen ≥15hrs/day**, to patients with severe resting hypoxemia in COPD, increases survival and improves the quality of life.

- **Indications for continuous long-term oxygen therapy** (LTOT) for patients with COPD → **i.e. indication for home oxygen**
  - **Saturation of oxygen (SaO_2) ≤ 88 %** or PaO_2 ≤ 55 mmHg (7.32 kPa) **confirmed twice over 3 weeks period**
  - In the presence of **Cor pulmonale; one of the following**
    - **SaO_2 ≤ 89 %** or PaO_2 ≤ 59 mmHg (7.85 kPa)
    - **Evidence of pulmonary hypertension** (ECG evidence of P pulmonale**)**
    - **Polycythemia (Hematocrit > 55 %) or**
    - **Clinical evidence of right heart failure (**peripheral edema suggesting CHF**)**
  - **Specific situations**
    - **SaO_2 ≥ 90 %** or PaO_2 ≥60 mmHg (7.98 kPa) with lung disease and other clinical needs such as sleep apnea with nocturnal **desaturation not corrected by CPAP.**
    - If the patient meets criteria at rest, O_2 should also be prescribed during sleep and exercise, and appropriately titrated.
    - If the patient is normoxemic at rest but desaturates during exercise (PaO_2 ≤55 mmHg [7.32 kPa]), O_2 is generally prescribed for use during exercise. For patients who desaturate (PaO_2 ≤55 mmHg [7.32 kPa]) during sleep, further evaluation with polysomnography may be indicated to assess for sleep-disordered breathing.

N.B.

- **The Only three interventions have been demonstrated to improve survival of patients with COPD are;**

  - Smoking cessation
  - Oxygen therapy in chronically hypoxemic patients, and
  - Lung volume reduction surgery (LVRS) in selected patients with emphysema.
- Oxygen is a drug that should be given with correct dosing and based on indication
  - Order example; ‘’put on Intranasal oxygen at a rate of 2 L/minute"



Chart; Relation between oxygen flow rate in L/min (X-axis) and the fraction of inspired oxygen (FiO2)/y-axis/. **Each additional L/min in oxygen flow increases the FiO2 by about 4 % (i.e. 24%, 28%, 32%... the difference in between is 4%). For example, if you put the patient in 2L/min, S/he will get 28% additional oxygen from the baseline SaO_2(On the other way, if the initial SaO_2 is 62 %, in order to make 90%, this patient will require additional 28 % oxygen which is 2L/min). If ≥ 10L/min is required, use face mask instead of Intra nasal cannula.**

D. Pulmonary rehabilitation:

- **Exercise** should be encouraged at all stages and patients reassured that breathlessness, while distressing, is not dangerous.
- **Physical training, disease education and nutritional counseling** reduce symptoms, improve health status and enhance confidence.

E. Pharmacologic therapies;

- These are used to reduced symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status.
- But, none of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.
- Pharmacologic therapy options for COPD include;
  - Bronchodilators
  - Steroids (ICS or OCS)

- **Combined ICS and bronchodilators**
- **Antibiotics**

A. **Bronchodilators** → *central to the symptomatic management of COPD.* They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms. Bronchodilators include;

- beta$_2$ /β_2/ agonists
    - β_2 agonists classified as
        - Short acting β_2 agonists **(SABA) → e.g. Salbutamol**
        - Long acting β_2 agonists **(LABA)** → **e.g. Salmeterol, Formoterol**
    - The effect of SABAs usually wears off in 4 - 6 hours whereas those LABAs have duration of action up to 12 hours.
    - SABA like **Salbutamol** may be used for patients with **mild disease** but LABA like **Salmeterol and Formoterol** inhalers are usually more appropriate for those with **moderate to severe disease**.
    - Regular and as needed SABAs or SAMAs improves symptoms and FEV1.
    - SABAs can also be used as needed (in between doses of LABAs).
- **Antimuscarinic (Anticholinergic) drugs**:
    - Short Acting Muscarinic Antagonist (**SAMA) like Ipratropium**
    - Long Acting Muscarinic Antagonist **(LAMA) like Tiotropium**
    - Ipratropium has a duration of action that is between 6 - 8 hours whereas Tiotropium lasts for up to 24 hours.
    - LAMAs generally improve symptoms and health status, and reduce exacerbations and related hospitalizations.
- **Oral bronchodilator therapy:**
    - **Methylxanthines** (e.g. **Theophylline/theophedrine** 120/11mg tablets) may be contemplated in patients who cannot use inhaled devices efficiently.

B. **Steroids (ICS or OCS)**

- Inhaled glucocorticosteroids **(ICS)** → **e.g. Beclomethasone, Fluticasone**
- Oral corticosteroids **(OCS) → e.g. prednisolone** 5mg tabs
    - Useful during exacerbations but maintenance therapy contributes to osteoporosis and impaired skeletal muscle function, and should be avoided.
    - Oral glucocorticoid trials assist in the diagnosis of asthma but do not predict response to inhaled glucocorticoids in COPD.

C. **Combined ICS and bronchodilators** → The FDC of an **ICS and a LABA (e.g. fluticasone with salmeterol, budesonide with formoterol)**

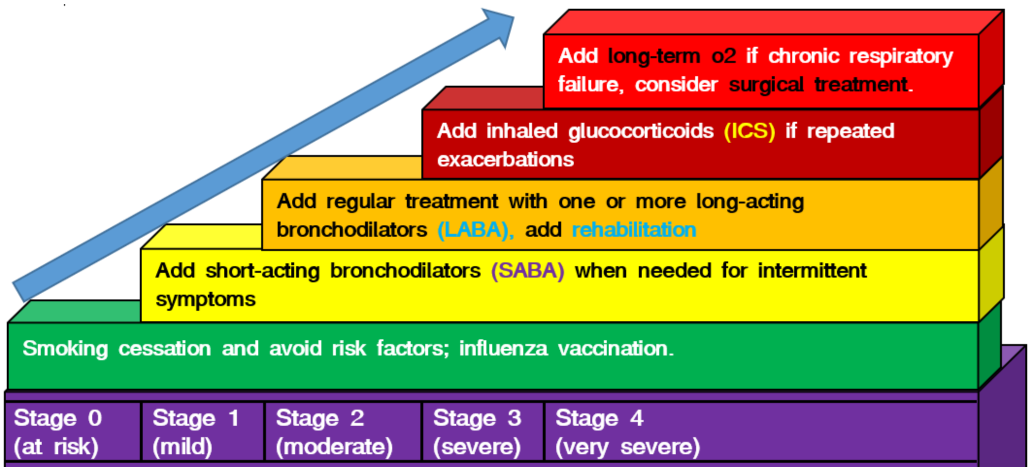
- Because there is no loose preparation of LABAs in the market, we generally tend to use combination of LABA/ICS.
- This combination improves lung function, reduces the frequency and severity of exacerbations and improves quality of life especially in patients with moderate to very severe COPD and exacerbations. These advantages may be accompanied by an increased risk of pneumonia, particularly in the elderly.
- **Use this combination especially** when there is;
    - History of hospitalization for exacerbation
    - ≥ 2 exacerbations per year

  - Blood eosinophils >300/µl or
  - History of (concomitant) asthma.

D. Antibiotics

- There are strong data implicating bacterial infection as a precipitant of a substantial portion of exacerbations.
- **Azithromycin**, chosen for both its anti-inflammatory and antimicrobial properties
  - **Azithromycin, 250mg, po daily or 500mg, 3x per week for prevention of exacerbations of COPD**
  - **Duration of prophylaxis in clinical studies was 01 year.**

Step-up Therapy based on GOLD staging


Add long-term o2 if chronic respiratory failure, consider surgical treatment.
Add inhaled glucocorticoids (ICS) if repeated exacerbations
Add regular treatment with one or more long-acting bronchodilators (LABA), add rehabilitation
Add short-acting bronchodilators (SABA) when needed for intermittent symptoms
Smoking cessation and avoid risk factors; influenza vaccination.
Stage 0 (at risk)
Stage 1 (mild)
Stage 2 (moderate)
Stage 3 (severe)
Stage 4 (very severe)

Figure; Step-up Therapy of COPD based on GOLD staging

Inhaled medication therapy based on grouping patients by severity of symptoms and risk of exacerbations.

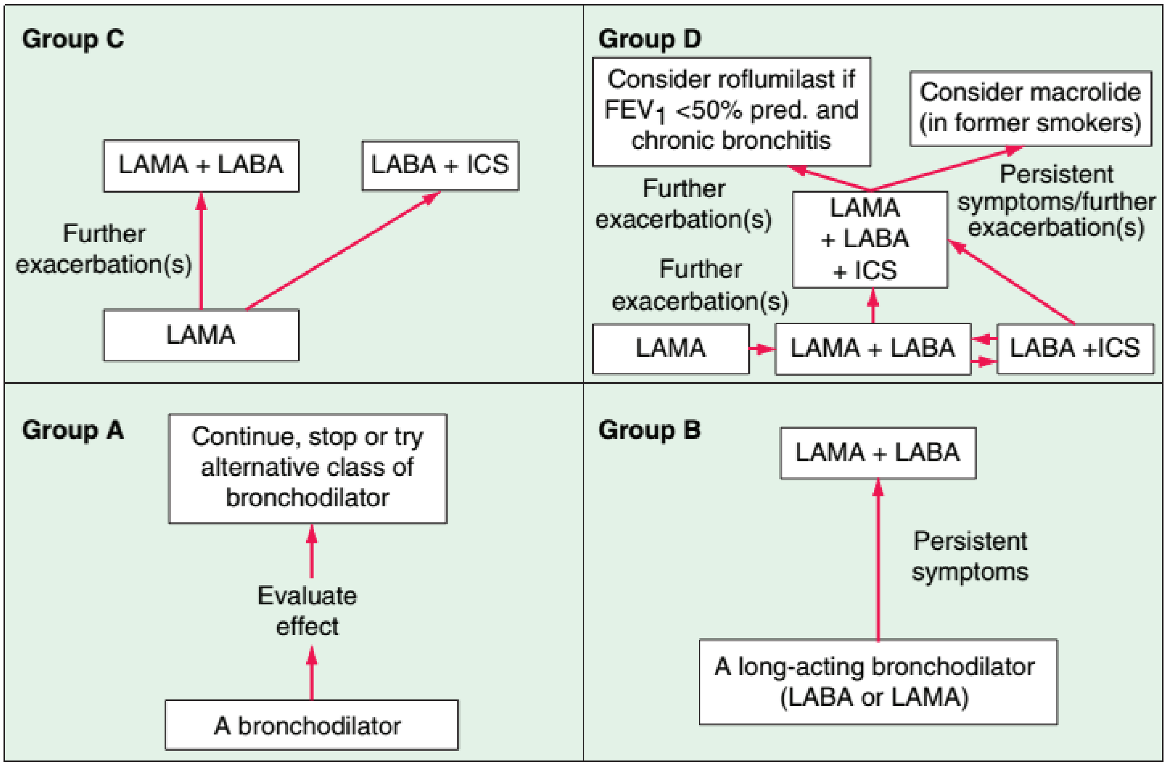

Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA
Group D
Consider roflumilast if FEV_1 <50% pred. and chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
Persistent symptoms/further exacerbation(s)
LAMA + LABA + ICS
Further exacerbation(s)
LAMA
LAMA + LABA
LABA +ICS
Group A
Continue, stop or try alternative class of bronchodilator
Evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

FIGURE 286-6 (Harrison 20th edition); Medication therapy for stable COPD. **Recommended pharmacologic treatment of stable COPD is based on respiratory symptoms and exacerbation frequency**.

Surgical management for carefully selected patients

- **Lung Volume Reduction Surgery (LVRS)** For patients with emphysema
  - Surgery, to remove the most emphysematous portions of lung, improves exercise, lung function, and survival.
  - Patients with **upper lobe-predominant emphysema and a low post-rehabilitation exercise capacity** are most likely to benefit from LVRS
  - Patients with an FEV1 <20% of predicted and diffusely distributed emphysema on CT scan have increased mortality after the procedure, and thus are not candidates for LVRS.

- **Lung Transplantation**
  - **COPD is currently the second leading indication** for lung transplantation.
  - candidates for lung transplantation should have;
    - very severe airflow limitation
    - severe disability despite maximal medical therapy, and
    - be free of significant comorbid conditions such as liver, renal, or cardiac disease.

2.2.1.1 Exacerbations of COPD

- Exacerbations are a prominent feature of the natural history of COPD.
- Exacerbations are **episodic acute worsening of respiratory symptoms**, including **increased dyspnea, cough, wheezing**, and/ or change in the amount and character of **sputum.**
- They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat.
- **The strongest single predictor of exacerbations is a history of a previous exacerbation**.
- **The frequency of exacerbations increases as airflow obstruction worsens**; patients with severe (FEV1 <50% predicted) or very severe airflow obstruction (FEV1 <30% predicted) on average have 1 - 3 episodes per year.
- However, some individuals with very severe airflow obstruction do not have frequent exacerbations.
- Other factors, such as an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT, and gastroesophageal reflux, are also associated with increased risk of COPD exacerbations.

Precipitating Causes

- A variety of stimuli may result in the final common pathway of airway inflammation and increased respiratory symptoms that are characteristic of COPD exacerbations.
- **Infection of tracheobronchial tree and air pollution are most common causes of COPD exacerbation**
  - **Bacterial infection/superinfection** is involved in >50% of exacerbations.
  - **Viral respiratory infections** are present in approximately 1/3rd of COPD exacerbations.
- **No specific precipitant can be identified,** In a significant minority of instances (20 - 35%). This figure increases up to 1/3rd of cases in our setup

Patient Approach

- **Establish the severity of the exacerbation as well as the severity of preexisting COPD.** The more severe either of these two components, the more likely that the patient will require hospital admission.
- The **history** should include;
  - Quantification of the degree and change in dyspnea
  - Fever
  - Change in character of sputum
  - Associated symptoms such as wheezing, nausea, vomiting, diarrhea, myalgias, and chills.
  - Frequency and severity of prior exacerbation.

- **The single greatest risk factor for hospitalization with an exacerbation is a history of previous hospitalization.**

- **Physical examination;**
  - An assessment of the degree of distress of the patient.
    - Tachycardia
    - Tachypnea
    - Use of accessory muscles
    - Signs of perioral or peripheral cyanosis
    - The ability to speak in complete sentences, and
    - The patient's mental status.
  - Chest examination
    - Focal findings
    - Degree of air movement
    - Wheezing
    - Asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and
    - Paradoxical motion of the abdominal wall.

- **DDX for COPD exacerbations → see Approach part of this chapter above**

- **Investigation**
  - **Chest x-ray or chest CT scan.**
    - For patients with severe underlying COPD, who are in moderate or severe distress, or those with focal findings
    - Approximately **25% of x-rays** in this clinical situation will be **abnormal**, with the most frequent findings being **pneumonia and CHF**.
  - Arterial blood-gas analysis
    - For patients with advanced COPD, a history of hypercarbia, mental status changes (confusion, sleepiness), or those in significant distress.
    - The presence of hypercarbia, defined as a PCO_2 >45 mmHg, has important implications for treatment (discussed below).
  - Pulmonary function test is not recommended

Management of exacerbations of COPD

- **Indication for admission**
  - New or worsening hypoxemia
  - Severe underlying disease
  - Those whose living situation is not conducive to careful observation and the delivery of prescribed treatment. (this is the commonest reason in our setup, and almost all patients need admission) and
  - Respiratory acidosis and hypercarbia

- Most COPD patients in our country are undiagnosed, a few of them are told they have ''bronchitis'' without confirmatory spirometry and still fewer have confirmed COPD.
  - Therefore, as discussed in patient approach part, COPD with acute exacerbation should be considered in every patient presenting with a recent worsening of his/her longstanding cough or dyspnea or sputum color change (purulence).

- **Non pharmacologic management principles are the same as stable COPD management (see above). These include;**
  - **Assessing and monitoring of the disease**
  - **Avoidance of modifiable risk factors/precipitant causes and vaccinations**
  - **Pulmonary rehabilitation.**

Pharmacologic management

- COPD exacerbations can be classified into 4 categories based on severity (look at GOLD severity classification above)
  - **Mild**: can be managed at **home with SABAs** only.
  - **Moderate**: can be managed as **outpatient** with **SABAs + antibiotics+ steroids**
  - **Severe without respiratory failure**: can be treated in the **wards** with **SABAs + antibiotics+ steroids.**
  - **Severe with respiratory failure**: **Needs ICU** admission for **Respiratory support** (Noninvasive or invasive ventilation).
    - ✓ Noninvasive intermittent positive pressure ventilation (NIPPV) in exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay.
- **Pharmacologic management Principles include;**
  - ***Oxygen therapy***
  - ***Bronchodilators*** → Inhaled bronchodilators (beta2-agonists and/or anticholinergics)
  - ***Corticosteroids***
  - ***Antibiotics*** → if there is features of airway infection (like increased volume/change of color of sputum, fever). **Identify and treat precipitant causes**

  - *? Mucolytic Agents*: a few patients with viscous sputum may benefit but the **widespread use cannot be recommended**
  - *? Antitussives*: Cough, a troublesome symptom in COPD, has a protective role. **Regular use of antitussives contraindicated**

1. *Oxygen therapy*
   - Deliver a flow rate of <15L/min.
   - Source of oxygen can be a cylinder (>99% pure oxygen) or oxygen concentrator (90% oxygen,10% nitrogen).
   - **Titrated to achieve a SaO_2 of 88-90%** to avoid oxygen induced hypercapnia.

- See the details from stable COPD management above

2. ***Bronchodilators***
   - Short acting bronchodilators:
     - Metered dose inhaler (MDI)= **Salbutamol** inhaler *(200 mcg/actuation):* 2-3 puffs every hour and then tapered to 2 puffs every 4hrs.
       - To read and watch video on how to use MDI, click here → How to use inhalers for asthma management
     - Nebulization of salbutamol or combined salbutamol/ipratropium bromide solution.
   - **Long-acting bronchodilators + ICS** → should be continued if patient was using them and should be started at discharge if they were not being used.

3. ***Corticosteroids***
   - **Only** used when having a significant exacerbation **(moderate or severe disease**), as they may lead to development of pneumonia and sepsis
   - Can be given **orally (prednisolone 40mg**) or **IV (hydrocortisone or methylprednisolone).** Oral and IV routes are equally effective
   - Recommended **for 5-7 days only**

4. ***Antibiotics***
   - Recommended **for moderate to severe illness or when the sputum is purulent.**
   - Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and/or fever) may benefit from antibiotic treatment.
   - Antibiotics are usually given **for 5-7days**
   - The specific antibiotic given should depend on the sensitivity pattern of the hospital.
     - Commonly **Augmentin (Amoxicillin/clavulanic acid)**, **cephalosporins, quinolones or macrolides** can be used.
   - Sputum culture is generally not helpful except in few conditions which may be associated with Gram negative infections like pseudomonas aeruginosa. Such as
     - Patient has recurrent exacerbation.
     - Patient is on invasive mechanical ventilation.

2.2.2 Asthma

→ Refer under short case of Nitsbin (click here → Asthma (አስም))

2.3 Suppurative lung diseases

- Suppurative Lung Diseases are group of pulmonary disorders that characterized by presence of **pus within the lung parenchyma**. These include;
  - Bronchiectasis
  - Lung abscess and
  - Empyema

- Here, we will discuss about Bronchiectasis and lung abscess. For Empyema, refer respiratory section from short case of Nitsbin (click here → **Empyema and Complicated Parapneumonic Effusions**)

2.3.1 Bronchiectasis

- *Bronchiectasis* refers to an **irreversible airway dilation that involves the lung in either a focal or a diffuse manner**
- Classically, it has been categorized as
  - Cylindrical or tubular (the most common form)
  - Varicose
  - Cystic
- It shares many clinical features with COPD, including inflamed and easily collapsible airways, obstruction to airflow, impaired clearance of secretions and frequent office visits and hospitalizations.

Etiology

- Bronchiectasis can arise from **infectious or noninfectious** causes
- Clues to the underlying etiology are often provided by the pattern of lung involvement.
- ***Focal bronchiectasis*** refers to bronchiectatic changes in a localized area of the lung and can be a consequence of obstruction of the airway. The cause may be;
  - **Extrinsic** (e.g., due to compression by **adjacent lymphadenopathy** or **parenchymal tumor mass**) or
  - **Intrinsic** (e.g., due to an **airway tumor** or **aspirated foreign body**, **Mucus Plugging (e.g. postoperative mucoid impaction**, a scarred/ stenotic airway, or bronchial atresia from congenital underdevelopment of the airway).
- ***Diffuse bronchiectasis*** is characterized by widespread bronchiectatic changes throughout the lung and often arises **from an underlying systemic or infectious disease process (i.e. acquired or congenital causes).**

  - ✓ **Acquired (~74%)**
    - **Infectious** → A variety of infections can cause bronchiectasis by destroying and damaging the bronchial walls and interfering with ciliary action.
      - Influenza, Adenovirus, Pertussis, Mycobacterium (M. TB, MAC)
      - Post TB fibrosis is the commonest cause in Ethiopia
      - **Recurrent infections** (airway obstruction, immunodeficiency, allergic bronchopulmonary aspergillosis, mycobacterium)

            - RVI (cause abnormal lung defense),
        - **Inflammatory**;
            - Gastric Aspiration
            - Autoimmune disease (RA, SLE, Crohn disease, Sjogren's Syndrome, etc.)
            - Ammonia
            - Neoplasm (not common)
            - ✓ Naturally will have faster course but Slower in carcinoids

    - ✓ **Congenital:**
        - Cystic fibrosis, Primary ciliary dyskinesia (e.g., Kartagener syndrome), Immunoglobulin deficiency (IgG, IgA...)
            - **Cystic fibrosis (CF) is the most common cause of bronchiectasis (accounts for half of all cases) world wide**
            - Have diffuse pattern commonly occur in upper lobes.
- ➢ **In many cases (25 - 50%),** the etiology of bronchiectasis is not determined **(idiopathic)**.

Pathophysiology

- **Induction of bronchiectasis requires two factors**:
    - An infectious insult
    - Impaired drainage, airway obstruction, or a defect in host defense
- The most widely cited mechanism of **infectious bronchiectasis** is the **"vicious cycle hypothesis,"** in which susceptibility to infection and poor mucociliary clearance result in microbial colonization of the bronchial tree.
    - The presence of the microbes incites continued chronic inflammation, with consequent damage to the airway wall, continued impairment of secretions and microbial clearance, and ongoing propagation of the infectious/inflammatory cycle.
    - Significant small-airway wall inflammation and larger-airway wall destruction as well as dilation, with loss of elastin, smooth muscle, and cartilage.
- Proposed mechanisms for **noninfectious bronchiectasis** include **immune-mediated reactions** that damage the bronchial wall (e.g., those associated with systemic autoimmune conditions such as SLE, RA…)
- ***Traction bronchiectasis*** refers to **dilated airways** arising from parenchymal distortion **as a result of lung fibrosis** (e.g., post radiation fibrosis or idiopathic pulmonary fibrosis).
- Site:
    - Left lung involved more than Right lung (Left to Right ratio = 9 : 7)
    - Left Lower lobe most frequently involved, Followed by Right middle lobe........Left upper lobe

Clinical Presentation:

- Most cases, onset is in childhood but, symptoms generally appear in 2nd - 3rd Decades
- Relatively common in females (F:M = 2.5 : 1.5)

- **The most common clinical presentation is a** persistent productive cough with ongoing production of thick, tenacious sputum **which may/may not be foul-smelling.**
- **Dyspnea**
- **Hemoptysis** → due to rupture of blood vessels near bronchial wall surfaces; usually mild and self-limited, but sometimes can be brisk and presents as an emergency
- **Crackles and wheezing** on lung auscultation
- **Clubbing** of the digits in some patients
- Acute exacerbations of bronchiectasis are usually **characterized by changes in the nature of sputum production, with increased volume and purulence.** However, typical signs and symptoms of lung infection, such as fever and new infiltrates, may not be present.
- **Evaluation of focal bronchiectasis almost always requires bronchoscopy to exclude airway obstruction** by an underlying mass or foreign body

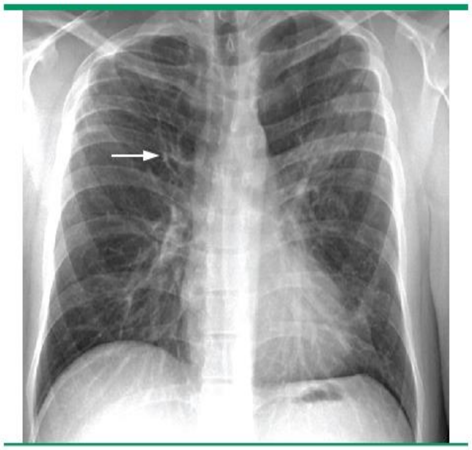
Diagnosis and Investigations

- The **diagnosis is usually clinically** (a persistent chronic cough and sputum production) **accompanied by consistent radiographic features.**

B. **CXR**

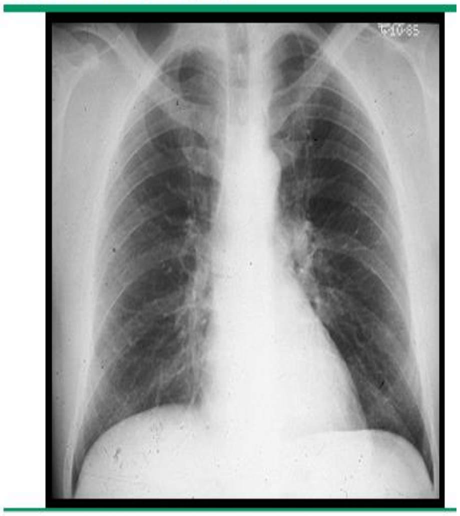
  - Although **chest radiographs lack sensitivity**, the presence of **"tram tracks" indicating dilated airways is consistent with bronchiectasis.**
  - CXR is abnormal in most cases, but findings are nonspecific. Suspicious, but non diagnostic radiographic findings include **linear atelectasis, dilated** and **thickened airways** and **irregular peripheral opacities** that may represent mucopurulent plugs.

Bronchiectasis



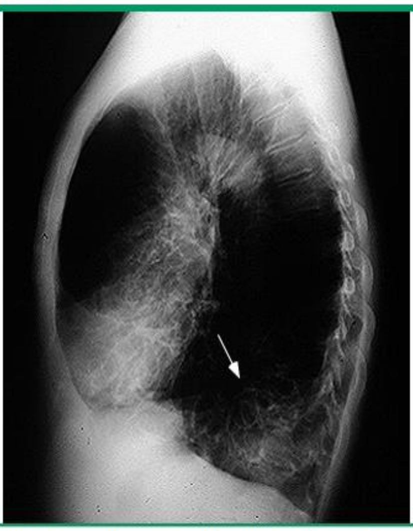
A posterior-anterior chest radiograph with walls of airways dilated and thickened (arrow) in the right upper lobe as seen in allergic bronchopulmonary aspergillosis. In the left upper lobe are airways filled with mucus and cellular debris.

Normal chest radiograph



Posteroanterior view of a normal chest radiograph.

Bronchiectasis

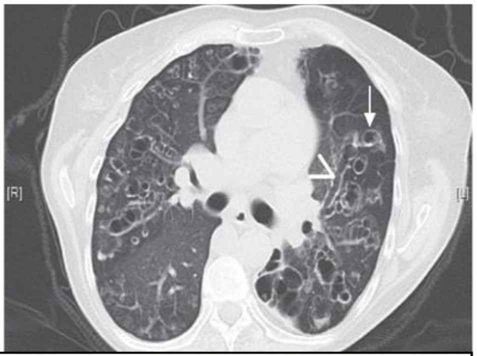


Lateral chest radiograph demonstrating ring shadows of cystic bronchiectasis (arrow).

Normal lateral chest radiograph

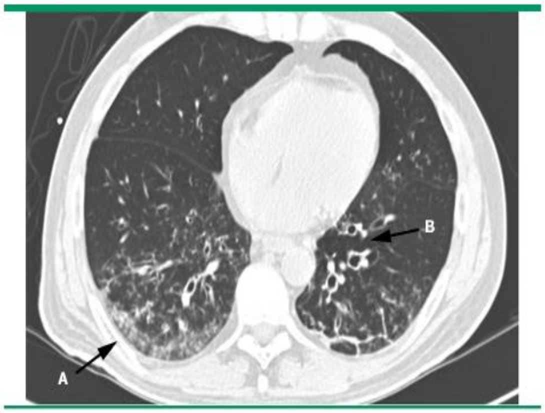
C. **High-resolution Chest CT → is Gold Standard diagnostic imaging (i.e.** more specific for bronchiectasis and is the imaging modality of choice for confirming the diagnosis.**).** CT findings include;

- Airway dilation (detected as parallel **"tram tracks" or as the "signet-ring sign"**–a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel)
- **Lack of bronchial tapering** (including the presence of tubular structures within 1 cm from the pleural surface)
- **Bronchial wall thickening** in dilated airways
- Inspissated secretions (e.g., the **"tree-in-bud" pattern**)
- **Cysts** emanating from the bronchial wall (especially pronounced in cystic bronchiectasis)



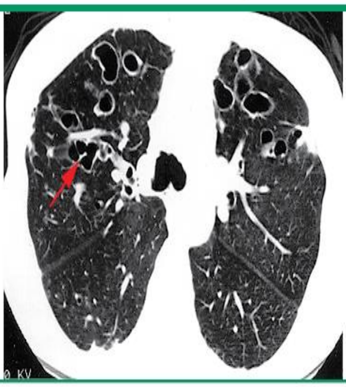
Picture; Representative chest CT image of severe bronchiectasis; This patient's CT demonstrates many severely dilated airways; seen both longitudinally *[arrowhead]* showing Trump truck sign (continuous non tapering airway with bronchial dilatation and bronchial wall thickening), and in cross-section *[arrow]* shows "signet-ring sign.*

Tree-in-bud



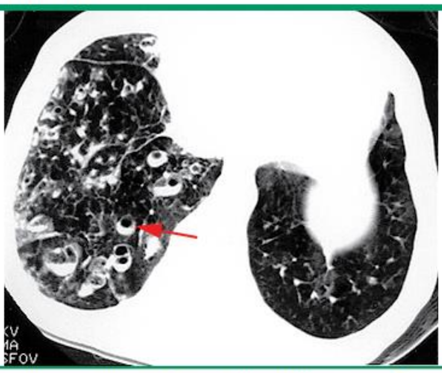
Chest CT with arrow A pointing to extensive tree-in-bud and arrow B of dilated and thickened airways.

Bronchiectasis with marked airway dilatation



HRCT shows clustering of markedly dilated airways in both upper lobes (arrow).

Bronchiectasis



High-resolution computerized tomography (HRCT) shows numerous ring shadows representing dilated airways in the right lung, many of which are partially filled with secretions (arrow).

D. **PFTs (if available)** reveal an obstructive pattern
  - Mild to moderate airflow obstruction is often detected on pulmonary function tests, overlapping with that seen at presentation with other conditions, such as COPD

E. **Laboratory tests**;
  - **CBC with differential** → supportive, if infectious cause is suspected, but may be normal
  - **Sputum smear** and culture for bacteria, mycobacteria, and fungi
    - **AFB or other TB diagnostic tests should be done, for a patient suspected with bronchiectasis, considering epidemiology of TB in Ethiopia**
  - Rheumatoid factor

F. Other laboratory tests (not available in our set up)
  - Immunoglobulin quantitation to measure the levels of the immunoglobulins IgG, IgM, and IgA and
  - Testing for cystic fibrosis: including Alpha-1 antitrypsin level and/or genotype
  - Specific aspergillus IgE and IgG antibodies, total serum IgE level
  - IgG subclass levels
  - Antibody titers to pneumococcal serotypes before and four weeks after vaccination with polysaccharide pneumococcal vaccine

Management of Bronchiectasis

- Conservative medical therapy
  - Mainstay of treatment for bronchiectasis is conservative medical therapy
  - Treatment of infectious bronchiectasis is **directed at the control of active infection and improvements in secretion clearance and bronchial hygiene** so as to decrease the microbial load within the airways and minimize the risk of repeated infections.
- Surgical management

1) **Medical therapy includes**

- **Stop smoking** (Tobacco Use) for smokers
- **Control Infection → Antibiotics for acute exacerbations and superimposed infections**
  - Superimposed infections are signaled by change in quality/quantity of sputum, fever, chest pain, etc.
  - **Antibiotics targeting the causative or presumptive pathogen** (with *Haemophilus influenzae* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations
  - Duration is usually for **a minimum of 7 - 10 days and perhaps for as long as 14 days.**
  - For severe cases; 2-3 weeks of IV followed by Oral (decreases morbidity, **controversial**)
- Eliminate reversible underlying cause
  - **TB → Anti TB**
  - **Foreign bodies → Remove**
  - Endobronchial Tumors → Remove (surgical)
  - Hypogammaglobinemia → Life Time IV supplementation
- Improve bronchial secretion clearance
  - **Chest physiotherapy** (postural drainage, chest percussion) to help remove the mucus
  - Mucolytic (N-acetyl cysteine, Recombinant DNase)
- Reverse air flow limitation by **Inhaled Bronchodilators (e.g. salbutamol)**
- **Consider oral/ systemic glucocorticosteroids (e.g. Prednisolone/prednisone, hydrocortisone)** as anti-inflammatory agents

2) **Surgical management**

- **Indication →refractory significant symptoms despite a prolonged medical trial**
- In select cases, surgery can be considered with;
  - **Resection of a focal area of suppuration.**
  - **Lung transplantation** → can be considered in advanced cases,
- Principles;
  - Seldom performed on children ≤ 2 yrs. Because of likelihood of improvement on medical therapy as the child grows
  - Priorities given to preservation of lung parenchyma
  - Exclude uncorrectable causes: Ciliary dyskinesia, multimodality
  - Use dual-lumen endotracheal tube may minimize spillage to contralateral lung
  - Segmentectomy or lobectomy, as indicated by anatomic involvement
  - Pneumonectomy is rarely indicated

- For bilateral disease, side with greater involvement is resected first (symptoms may sufficiently improve to preclude resection of opposite side)
- For those ultimately requiring bilateral resection, an interval 6 -12 months is generally recommended to allow adequate recovery and evaluation of symptoms

2.3.2 Lung Abscess

Dr. Mulualem. G

- *Lung abscess (a.k.a* necrotizing pneumonia*)* represents **necrosis and cavitation of the lung following microbial infection.**
- Lung abscesses can be **single or multiple** but usually are marked by **a single dominant cavity >2 cm in diameter** *(> 6 cm is poor prognostic sign).*
- Most cases of lung abscess may be due to complications of aspiration pneumonia by anaerobic microorganisms present in the gingival cervices.
- In general, middle-aged men are more commonly affected than middle-aged women *(age > 60 is poor prognostic sign)*

Risk factors for primary lung abscess

- **Aspiration → The major risk factor for primary lung abscesses**. Patients at particular risk for aspiration include;
    - Those with altered mental status
    - Prior cerebrovascular or cardiovascular events
    - Seizures
    - Esophageal dysmotility or esophageal lesions (strictures or tumors)
    - Gastric distention and/or GERD, especially those who spend substantial time in the recumbent position
    - Alcoholism
    - Drug overdose
    - Bulbar dysfunction
    - Neuromuscular disease.

Etiology and pathogenesis

- Lung abscesses are usually **characterized as either primary (~80% of cases) or secondary**.
- ***Primary* lung abscesses usually arise from aspiration,** are often caused principally by **anaerobic bacteria**, and occur in the absence of an underlying pulmonary or systemic condition.
    - The development of primary lung abscesses is thought to originate when chiefly anaerobic bacteria in the gingival crevices are aspirated

  into the lung parenchyma in a susceptible host
  - Pneumonitis develops initially (exacerbated in part by tissue damage caused by gastric acid); then, over a period of 7 - 14 days, the anaerobic bacteria produce parenchymal necrosis and cavitation
- ***Secondary* lung abscesses** arise in the setting of an underlying condition, such as; **A post obstructive process** (e.g., a bronchial foreign body or tumor) **or A systemic process** (e.g., HIV infection or another immunocompromising condition).
  - The pathogenesis of secondary abscesses depends on the predisposing factor. For example, in cases of bronchial obstruction from malignancy or a foreign body, the obstructing lesion prevents clearance of oropharyngeal secretions, leading to abscess development.
  - With underlying systemic conditions (e.g., immunosuppression), impaired host defense mechanisms lead to increased susceptibility to the development of lung abscesses caused by a broad range of pathogens, including opportunistic organisms
  - Lung abscesses also arise from septic emboli
- Lung abscesses can also be characterized as **acute (< 4 - 6 weeks in duration) or chronic (~40% of cases).**
  - Symptom duration of > 8 weeks is poor prognostic sign
- **Examples of Microbial Pathogens That Can Cause Lung Abscesses include;**
  - Primary lung abscess (usually with risk factors for aspiration)
    - Often polymicrobial, primarily including **Anaerobes** (e.g., *Peptostreptococcus* spp, *Bacteroides* spp) as well as microaerophilic **streptococci**
  - Secondary lung abscess (often with underlying immunocompromise)
    - ***Staphylococcus aureus*** *→ can arise from* Embolic lesions (often from endocarditis)
    - ***Pseudomonas aeruginosa → most common***
    - Enterobacteriaceae)
    - *Nocardia* spp., *Aspergillus* spp., *Cryptococcus* spp, *Legionella* spp.
    - *PCP (Pneumocystis jirovecii)*
  - Endemic infections (with or without underlying immunocompromise)
    - *M. tuberculosis* (as well as MAC)
    - *Histoplasma capsulatum*, *Coccidioides, Blastomyces* spp.,
    - parasites (e.g., *Entamoeba histolytica*, *Strongyloides stercoralis*)

Clinical features

- Clinical manifestations may initially be similar to those of pneumonia, with fevers, cough, sputum production, and chest pain
- **Copious putrid or malodorous sputum is typical for anaerobic infection and common in lung abscess.**
  - Offensive sputum to the extent bad odor disturbing those in the house

or ward where the sputum is collected.

- Absence of chills or rigors. But Patients with lung abscesses due to non-anaerobic organisms, such as *S. aureus*, may present with a more fulminant course characterized by high fevers and rapid progression.
- Hemoptysis or pleurisy
- A more chronic and indolent systemic presentation that includes night sweats, fatigue, and anemia is often observed with anaerobic lung abscesses.
- Findings on physical examination may include;
  - Fevers
  - Poor dentition, and/or gingival disease
  - Amphoric and/or cavernous breath sounds on lung auscultation.
  - Digital clubbing and the absence of a gag reflex.

Differential diagnosis

- Noninfectious processes that result in cavitary lung lesions, include;
  - Lung infarction
  - Malignancy
  - Sequestration
  - Cryptogenic organizing pneumonia
  - Sarcoidosis
  - Vasculitides and other autoimmune diseases (e.g., granulomatosis with polyangiitis)
  - Lung cysts or bullae containing fluid
  - Septic emboli (e.g., from tricuspid valve endocarditis)

Complications of lung abscess

- Larger cavity size on presentation may correlate with the development of persistent cystic changes **(pneumatoceles) or bronchiectasis**.
- Additional possible complications include
  - **Recurrence** of abscesses despite appropriate therapy
  - Extension to the pleural space with development of **empyema**
  - **Life-threatening hemoptysis**, and
  - **Massive aspiration of lung abscess contents.**

Investigations and diagnosis

1. CXR
   - a thick-walled cavity with an air-fluid level
   - pulmonary infiltrates with cavity confirm diagnosis in majority of patients.

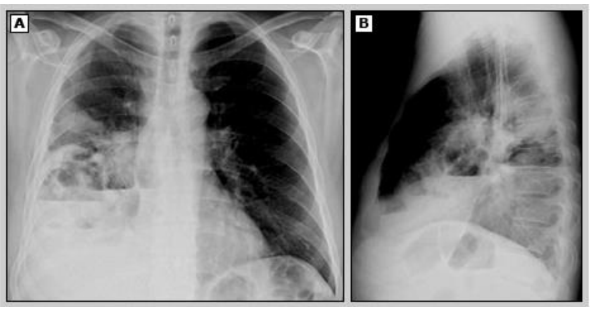


Image 1, Lung abscess; PA (A) and lateral (B) CXR show areas of **consolidation** and several **air-fluid levels** within the right lower lobe. Less extensive consolidation is evident in the right middle lobe.

2. CT scan
   - CT permits **better anatomic definition** than CXR and may provide earlier evidence of cavitation.
   - CT may also yield additional information regarding a possible **underlying cause of lung abscess**, such as malignancy
   - May help **to distinguish a peripheral lung abscess from a pleural infection**.
     - This distinction has important implications for treatment because a pleural space infection, such as an empyema, may require urgent drainage.
   - But in our setup CT is too costly for most patients and it is better to diagnose clinically and with CXR findings

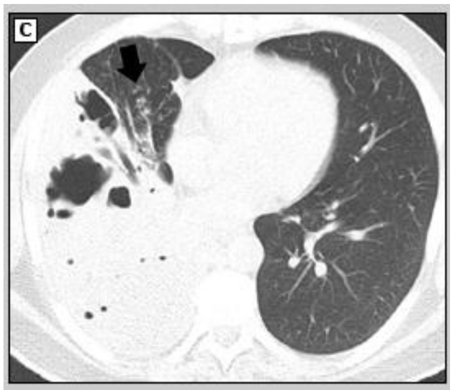
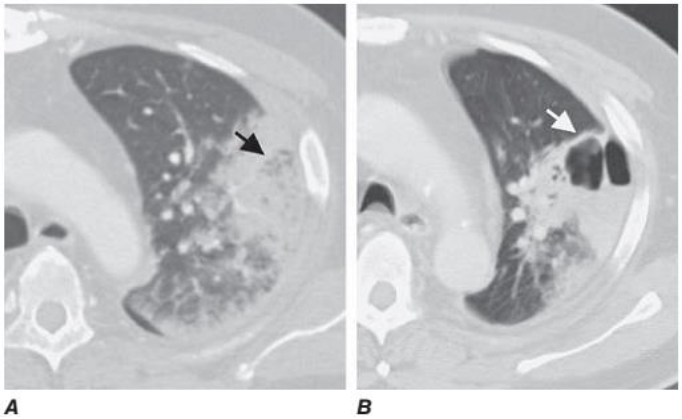


Image 2, Lung abscess; **CT image of the above pt** confirms the CXR findings and also demonstrates a few **centrilobular nodules in the right middle lobe (black arrow).** The patient was a 50-year-old man with pneumonia due to anaerobic organisms.



Figure; **Representative chest CT scans demonstrating development of lung abscesses**. This patient was immunocompromised by underlying lymphoma and developed severe *Pseudomonas aeruginosa* pneumonia, as represented by a left lung infiltrate with concern for **central regions of necrosis** (***panel A, black arrow***). Two weeks later, areas of **cavitation with air-fluid levels** were visible in this region and were consistent with the development of lung abscesses (***panel B, white arrow***).

3. **Gram stain and culture** of expectorated sputum → contaminations is likely, may indicate upper airway pathogens than the lower, may be negative if antibiotic already started
4. **AFB and KOH** examination of sputum → if TB or fungal causes are considered.
5. **Pleural fluid analysis** → click here → pleural fluid analysis
6. **Blood cultures** → When a secondary lung abscess is present or empirical therapy fails to elicit a response, sputum and blood cultures are advised

NB: the isolation of anaerobic microorganisms from lung infections is usually challenging (rarely grow from blood samples and mostly contaminated from sputum and aspirates), except for empyema patients.

Treatment of lung abscess

Principles of management include;

- Chest physiotherapy and postural drainage
- Empiric antibiotic therapy
- Surgery in selected cases

Empiric antibiotic therapy for lung abscess

- Anaerobic coverage is imperative regardless of culture (both strict and facultative anaerobes) *Since Mixed infection (anaerobes and facultative anaerobes like oral streptococci*) is common in lung abscess.
- If non oral floral pathogen is detected from microbiologic reports, tailor treatment to the specific microorganism.

First line

- ✓ Ampicillin-sulbactam 1.5 - 3 g IV QID.
  - **Once the patient's condition is stable, change to oral Augmentin (amoxicillin-clavulanate)**
  - This therapy should be continued until imaging demonstrates that the lung abscess has cleared or regressed to a small scar.
  - **Treatment duration may range from 3 - 4 weeks to as long as 14 weeks (usually 4-8 weeks)**

Second line → duration for 4-8 weeks or longer until the abscess radiologically resolves

- ✓ Ceftriaxone (1g IV BID or 2 g IV daily) or

- ✓ Penicillin G 1 - 2 million units IV QID or
- ✓ Cefotaxime 1 or 2 g IV TID

  plus
- ✓ Metronidazole 500 mg PO TID
  - N.B Notably, **metronidazole is not effective as a single agent**: it covers anaerobic organisms but not the microaerophilic streptococci. **So, combination with penicillin's is mandatory**
- ☛ For penicillin-allergic patients
  - Clindamycin, 600 mg, IV, TID then, with the disappearance of fever and clinical improvement, 300 mg PO QID

Parenteral-to-Oral Switch of antibiotics:

- After treatment with intravenous antibiotics for the first 2-3 weeks or until significant resolution of symptoms, patients can be treated with oral antibiotics until the end of treatment.
- **Augmentin (Amoxicillin + clavulanic acid)**, 625mg P.O TID is the **preferred** agent.
- **Clindamycin**, 300mg P.O, QID[9] is an **alternative** otherwise the choice may be guided by the susceptibility data available.

Follow up

- Do **weekly or 2 times per week CXR** in patients showing clinical improvement, with discontinuation of therapy when the radiograph is clear or there is a small, stable, residual lesion

Surgical management

Indication;

- **Patients who do not respond to antibiotics** and whose additional **diagnostic studies fail to identify an additional pathogen** that can be treated

Treatment Options include;

- **Surgical resection** and
- **Percutaneous drainage** of the abscess → especially when the patient is a poor surgical candidate.

Timing of surgical intervention can be challenging;

- The goal is to balance the morbidity/mortality risk of a procedure with the need for definitively clearing the abscess in the setting of persistent infection that is not responsive to nonsurgical approaches.

Possible complications of percutaneous drainage include

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[9] *This dose if from Harrison 20th edition. 2021 national STG guideline for General hospitals of Ethiopia recommend ''Clindamycin 600mg, PO, TID''*

- Bacterial contamination of the pleural space
- Pneumothorax
- Hemothorax.

Prognosis

- **Mortality rates for secondary abscesses are generally higher–as high as 75%,** while rates for primary abscesses have been as low as 2%
- Other **poor prognostic factors** include;
    - Age of > 60 years
    - The presence of aerobic bacteria
    - Sepsis at presentation
    - Symptom duration of >8 weeks, and
    - Abscess size of >6 cm.

Prevention

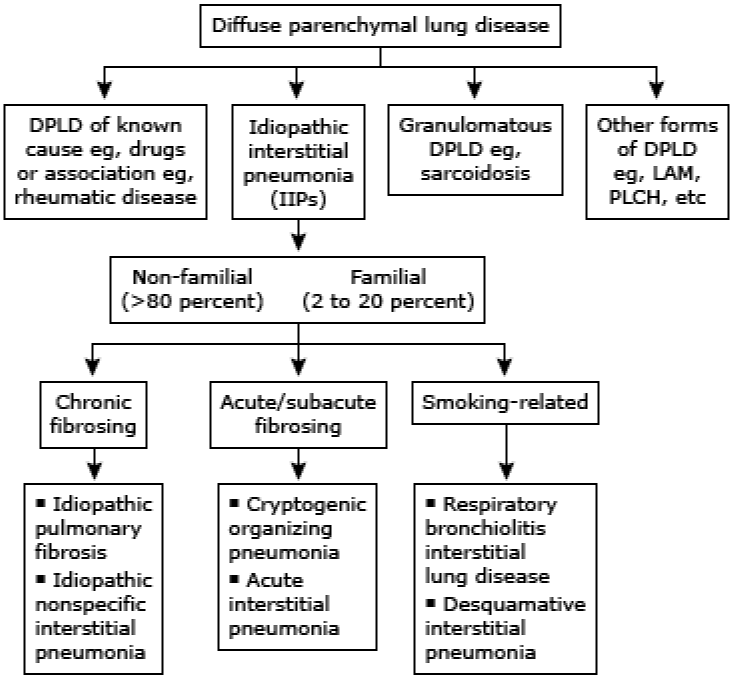
- Mitigation of underlying risk factors may be the best approach to prevention of lung abscesses, with attention directed toward;
    - Airway protection
    - Oral hygiene, and
    - Minimized sedation with elevation of the head of the bed for patients at risk for aspiration.
- Prophylaxis against certain pathogens in at-risk patients (e.g., recipients of bone marrow or solid organ transplants or patients whose immune systems are significantly compromised by HIV infection) may be undertaken.

2.4 ILD (Interstitial Lung disease)

Dr. Asmare. W

- ILDs (also known as diffuse parenchymal lung diseases) represent a large number of conditions that involve the parenchyma of the lung–the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between those structures–as well as the perivascular and lymphatic tissues.
- The disorders in this heterogeneous group are classified together because of similar clinical, roentgenographic, physiologic, or pathologic manifestations.
- ILDs have been difficult to classify because >200 known individual diseases are characterized by diffuse parenchymal lung involvement, either as the primary condition or as a significant part of a multiorgan process, as may occur in the connective tissue diseases (CTDs).

- Sarcoidosis, **idiopathic pulmonary fibrosis (IPF)**(*is the most common form of idiopathic interstitial pneumonia),* and pulmonary fibrosis associated with CTDs the most common ILDs of unknown etiology.
- Among the ILDs of known cause, the largest group includes occupational and environmental exposures, especially the inhalation of inorganic dusts, organic dusts, and various fumes or gases.
- ILD can also complicate the course of most of the connective tissue diseases (eg, polymyositis/dermatomyositis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disease).

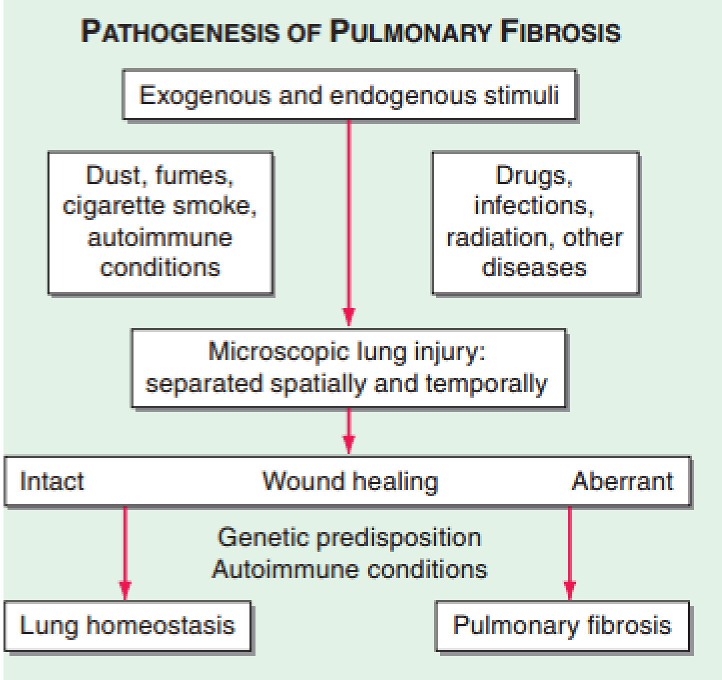

Diffuse parenchymal lung disease
DPLD of known cause eg, drugs or association eg, rheumatic disease
Idiopathic interstitial pneumonia (IIPs)
Granulomatous DPLD eg, sarcoidosis
Other forms of DPLD eg, LAM, PLCH, etc
Non-familial (>80 percent)
Familial (2 to 20 percent)
Chronic fibrosing
Acute/subacute fibrosing
Smoking-related
▪ Idiopathic pulmonary fibrosis
▪ Idiopathic nonspecific interstitial pneumonia
▪ Cryptogenic organizing pneumonia
▪ Acute interstitial pneumonia
▪ Respiratory bronchiolitis interstitial lung disease
▪ Desquamative interstitial pneumonia

PATHOGENESIS

- The ILDs are nonmalignant disorders and are not caused by identified infectious agents.
- The precise pathway(s) leading from injury to fibrosis is not known. Although there are multiple initiating agent(s) of injury, the immunopathogenic responses of lung tissue are limited, and the mechanisms of repair have common features.
- the two major histopathologic patterns are a granulomatous pattern and a pattern in which inflammation and fibrosis predominate;
- **Granulomatous Lung Disease**
  - This process is characterized by an accumulation of T lymphocytes, macrophages, and epithelioid cells organized into discrete structures (granulomas) in the lung parenchyma.

  - The granulomatous lesions can progress to fibrosis. Many patients with granulomatous lung disease remain free of severe impairment of lung function or, when symptomatic, improve after treatment.
  - The main differential diagnosis is between sarcoidosis and hypersensitivity pneumonitis.

- **Inflammation and Fibrosis**
  - The initial insult is an injury to the epithelial surface that causes inflammation in the air spaces and alveolar walls.
  - If the disease becomes chronic, inflammation spreads to adjacent portions of the interstitium and vasculature and eventually causes interstitial fibrosis. Important histopathologic patterns found in the ILDs include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia, respiratory bronchiolitis/desquamative interstitial pneumonia, organizing pneumonia, diffuse alveolar damage (acute or organizing), and lymphocytic interstitial pneumonia.


PATHOGENESIS OF PULMONARY FIBROSIS
Exogenous and endogenous stimuli
Dust, fumes, cigarette smoke, autoimmune conditions
Drugs, infections, radiation, other diseases
Microscopic lung injury: separated spatially and temporally
Intact
Wound healing
Aberrant
Genetic predisposition
Autoimmune conditions
Lung homeostasis
Pulmonary fibrosis

Proposed mechanism for the pathogenesis of pulmonary fibrosis.

- The lung is naturally exposed to repetitive injury from a variety of exogenous and endogenous stimuli.
- Several local and systemic factors (e.g., fibroblasts, circulating fibrocytes, chemokines, growth factors, and clotting factors) contribute to tissue healing and functional recovery.
- Dysregulation of this intricate network through genetic predisposition, autoimmune conditions, or superimposed diseases can lead to aberrant wound healing, with the result of pulmonary fibrosis. Alternatively, excessive injury to

the lung may overwhelm even intact reparative mechanisms and lead to pulmonary fibrosis.

CLINICAL PRESENTATION

- Patients with ILD commonly come to clinical attention in one of the following ways:
    - Symptoms of progressive breathlessness with exertion (dyspnea) or a persistent nonproductive cough.
    - Pulmonary symptoms associated with another disease, such as a connective tissue disease.
    - History of occupational exposure (e.g, asbestosis, silicosis)
    - An abnormal chest imaging study
    - Lung function abnormalities on simple office spirometry, particularly a restrictive ventilatory pattern (i.e. reduced total lung capacity and forced vital capacity).
- The most important step in the initial evaluation of a patient with suspected interstitial lung disease is obtaining a complete history.
- Careful documentation of the past medical history is important in the initial assessment because the cause of the illness is often recognized from the patient's history.
- In addition to a thorough review of past systemic conditions and HIV risk factors, several other aspects of the history are particularly important and include the following features.

Duration of Illness;

- **Acute presentation** (days to weeks)
    - although unusual, occurs with allergy (drugs, fungi, helminths), acute interstitial pneumonia (AIP), eosinophilic pneumonia, and hypersensitivity pneumonitis. These conditions may be confused with atypical pneumonias because of diffuse alveolar opacities on chest x-ray.
- **Subacute presentation** (weeks to months)
    - may occur in all ILDs but is seen especially in sarcoidosis, drug-induced ILDs, the alveolar hemorrhage syndromes, cryptogenic organizing pneumonia (COP), and the acute immunologic pneumonia that complicates systemic lupus erythematosus (SLE) or polymyositis.
- **chronic presentation** (months to years).
    - In most ILDs, the symptoms and signs form a chronic presentation
    - Examples include IPF, sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH), pneumoconiosis, and CTDs.

  - Episodic presentations are unusual and include eosinophilic pneumonia, hypersensitivity pneumonitis, COP, vasculitides, pulmonary hemorrhage, and Churg-Strauss syndrome.

Age

- Most patients with sarcoidosis, ILD associated with CTD, lymphangioleiomyomatosis (LAM), PLCH, and inherited forms of ILD (familial IPF, Gaucher disease, Hermansky-Pudlak syndrome) present between the ages of 20 and 40 years.
- Most patients with IPF are older than 60 years

Smoking History

- 2/3rd to 75% of patients with IPF and familial lung fibrosis have a history of smoking.
- Patients with PLCH, respiratory bronchiolitis/desquamative interstitial pneumonia (DIP), Goodpasture syndrome, respiratory bronchiolitis, and pulmonary alveolar proteinosis are usually current or former smokers.

Prior medication use and irradiation

- A detailed history of all medications taken and any exposure to therapeutic irradiation is needed to exclude the possibility of drug-induced or radiation-induced lung disease.

Other Important Past History

- Parasitic infections may cause pulmonary eosinophilia, and therefore a travel history should be taken in patients with known or suspected ILD.
- History of risk factors for HIV infection should be elicited because several processes may occur at the time of initial presentation or during the clinical course, e.g., HIV infection, organizing pneumonia, AIP, lymphocytic interstitial pneumonitis, and diffuse alveolar hemorrhage.

Symptoms

- Patients with ILD can present with a number of symptoms, and it is important to ascertain the duration, severity, and progression of symptoms.
- Most of the symptoms are nonspecific, but some will help to narrow the differential. In particular, patients should be asked about extrapulmonary symptoms that might suggest a systemic disorder.
- **Dyspnea**
  - Dyspnea is a common complaint of patients with cardiac or pulmonary disease.
  - In most instances, the patient has attributed the insidious onset of breathlessness with exertion to aging, deconditioning, obesity, or a

previous unresolved upper respiratory tract illness. However, some patients, especially those with sarcoidosis, silicosis, or pulmonary Langerhans cell histiocytosis, may have extensive parenchymal lung disease on chest radiograph **without** significant dyspnea. This most often occurs early in the course of the disease.

- **Cough**
  - **A dry cough is common** and can be particularly bothersome in conditions that involve the airways, such as sarcoidosis, bronchiolitis obliterans with or without organizing pneumonia, respiratory bronchiolitis, pulmonary Langerhans cell histiocytosis, hypersensitivity pneumonitis, lipoid pneumonia, and lymphangitic carcinomatosis.
  - **A productive cough is** unusual **for most ILDs**; rarely, a mucoid, salty-tasting sputum is reported by patients with bronchoalveolar cell carcinoma.
- **Hemoptysis**
  - Grossly bloody or blood-streaked sputum may occur in the diffuse alveolar hemorrhage syndromes, lymphangioleiomyomatosis, tuberous sclerosis, pulmonary veno-occlusive disease, longstanding mitral valve disease, and granulomatous vasculitides.
  - In some patients, diffuse alveolar bleeding may be present without hemoptysis; the clinical manifestations in such patients may be dyspnea and an iron deficiency anemia. The new onset of hemoptysis in a patient with known ILD suggests a complicating malignancy.
- **Wheezing**
  - Wheezing is an **uncommon** manifestation of ILD.
  - It has been described in cases of lymphangitic carcinomatosis, chronic eosinophilic pneumonia, EGPA, and respiratory bronchiolitis.
- **Chest pain**
  - Chest pain is **uncommon** in most ILDs. However, pleuritic chest pain may occur in ILD associated with rheumatoid arthritis, SLE, mixed connective tissue disease, and some drug-induced disorders.
  - In addition, the acute onset of pleuritic chest pain may indicate a pneumothorax. Substernal discomfort or pain is common in sarcoidosis.
- **Extrapulmonary symptoms**
  - Clinical findings suggestive of a connective tissue disease should be carefully recorded. These include *musculoskeletal pain, weakness, fatigue, fever, joint pains or swelling, photosensitivity, Raynaud phenomenon, pleuritis, dry eyes, and dry mouth.* However, the absence of these symptoms does not exclude connective tissue disease, as the pulmonary manifestations occasionally precede the more typical systemic manifestations by months or years (especially in rheumatoid arthritis, systemic lupus erythematosus, and polymyositis-dermatomyositis).

DIAGNOSIS

- **LABORATORY TESTS**
    - The routine laboratory evaluation of suspected ILD typically includes
        - **LFT**
        - **RFT**
        - **CBC With differentials** → to check for evidence of anemia, polycythemia, leukocytosis, or eosinophilia
        - **Urinalysis.**
    - LDH → A raised LDH level is a nonspecific finding common to ILDs.
    - Antinuclear antibodies and anti-immunoglobulin antibodies (rheumatoid factors) → are identified in some patients, even in the absence of a defined CTD.
    - serum level of ACE → commonly Elevated in ILDs, especially sarcoidosis.
    - Serum precipitins confirm exposure when hypersensitivity pneumonitis is suspected, although they are not diagnostic of the process.
    - Antineutrophil cytoplasmic or anti-basement membrane antibodies are useful if vasculitis is suspected.

IMAGING

- **Chest radiography**
    - The most common radiographic abnormality on routine chest radiograph is **a reticular pattern**; however, nodular or mixed patterns (alveolar filling and increased interstitial markings) are not unusual.
    - Subgroups of ILDs exhibit **nodular opacities with a predilection for the upper lung zones** (sarcoidosis, PLCH, chronic hypersensitivity pneumonitis, silicosis, berylliosis, RA [necrobiotic nodular form], ankylosing spondylitis).
    - Although the chest radiograph is useful in suggesting the presence of interstitial lung disease (ILD), the correlation between the radiographic pattern and the stage of disease (clinical or histopathologic) is generally poor.
    - Only the radiographic finding of **honeycombing (small cystic spaces)** correlates with pathologic findings and, when present, portends a poor prognosis.
    - The chest radiograph is **normal in as many as 10 percent of patients** with some forms of ILD, particularly those with hypersensitivity pneumonitis.
- HRCT
    - Should be obtained in almost all patients with diffuse pulmonary parenchymal disease.

  - obtain both supine and prone images to avoid confusing dependent atelectasis with interstitial opacities.
  - Comparing inspiratory and expiratory views is helpful when bronchiolitis is suspected.
  - HRCT is **superior to the plain chest x-ray for early detection and confirmation of suspected ILD.**
  - In addition, HRCT allows **better assessment of the extent and distribution of disease, and it is especially useful in the investigation of patients with a normal chest radiograph.**
  - Coexisting disease is often best recognized on HRCT scanning, e.g., mediastinal adenopathy, carcinoma, or emphysema.
  - Some features to be expected in HRCT include
    - Infiltration (nodular, cyst)
    - honey comb appearance
    - collapsing lung
    - pleural thickening
    - ground glass appearance
- **ECG**
  - usually normal unless pulmonary hypertension is present; then it demonstrates right-axis deviation, right ventricular hypertrophy, or right atrial enlargement or hypertrophy.
- **Echo →** also reveals right ventricular dilation and/or hypertrophy in the presence of pulmonary hypertension.

PULMONARY FUNCTION TESTING

- **Spirometry and Lung Volumes**
  - Measurement of lung function is important in assessing the extent of pulmonary involvement in patients with ILD.
  - Most forms of ILD produce a **restrictive defect** with reduced total lung capacity (TLC), functional residual capacity, and residual volume.
  - Measurement of lung function is most helpful for assessing the severity of lung involvement and the pattern, whether obstructive, restrictive, or mixed.
  - The pattern is useful in narrowing the number of possible diagnoses.
  - arterial blood gases are often obtained to corroborate results of pulse oximetry
  - FEV1 and FVC are reduced, but these changes are related to the decreased TLC.
  - The FEV1/FVC ratio is usually normal or increased.

  - Lung volumes decrease as lung stiffness worsens with disease progression.
- **Diffusing Capacity**
  - A reduction in the diffusing capacity of the lung for carbon monoxide (DlCO) is a common but nonspecific finding in most ILDs.
  - This decrease is due in part to effacement of the alveolar capillary units but, more important, to mismatching of ventilation and perfusion (V/Q).
  - Lung regions with reduced compliance due to either fibrosis or cellular infiltration may be poorly ventilated but may still maintain adequate blood flow, and the ventilation-perfusion mismatch in these regions acts like true venous admixture.
  - The severity of the reduction in DlCO does not correlate with disease stage.

Role of Bronchoalveolar lavage (BAL)

- BAL is performed during flexible bronchoscopy to obtain samples of cells and fluid from the distal airways and alveoli.
- The lavage fluid is sent for cell counts; cultures for mycobacterial, viral, and fungal pathogens; and cytologic analysis.
- BAL is particularly useful in the evaluation of patients with ILD that is associated with **hemoptysis**, is acute or rapidly progressive, or is likely caused by one of the following diseases: sarcoidosis, hypersensitivity pneumonitis, pulmonary Langerhans histiocytosis, or infection.
- For patients with a subacute or chronic presentation of ILD, BAL is often performed when sarcoidosis, hypersensitivity pneumonitis, pulmonary Langerhans cell histiocytosis (PLCH), or infection are suspected based on the radiographic pattern (eg, upper lobe predominance of reticular opacities, hilar lymphadenopathy, irregular cystic airspaces), history of exposure (eg, bird keeping, farming), or concomitant clinical findings (eg, hemoptysis, renal insufficiency).
- BAL does not have an established role in the assessment of ILD progression or response to therapy.

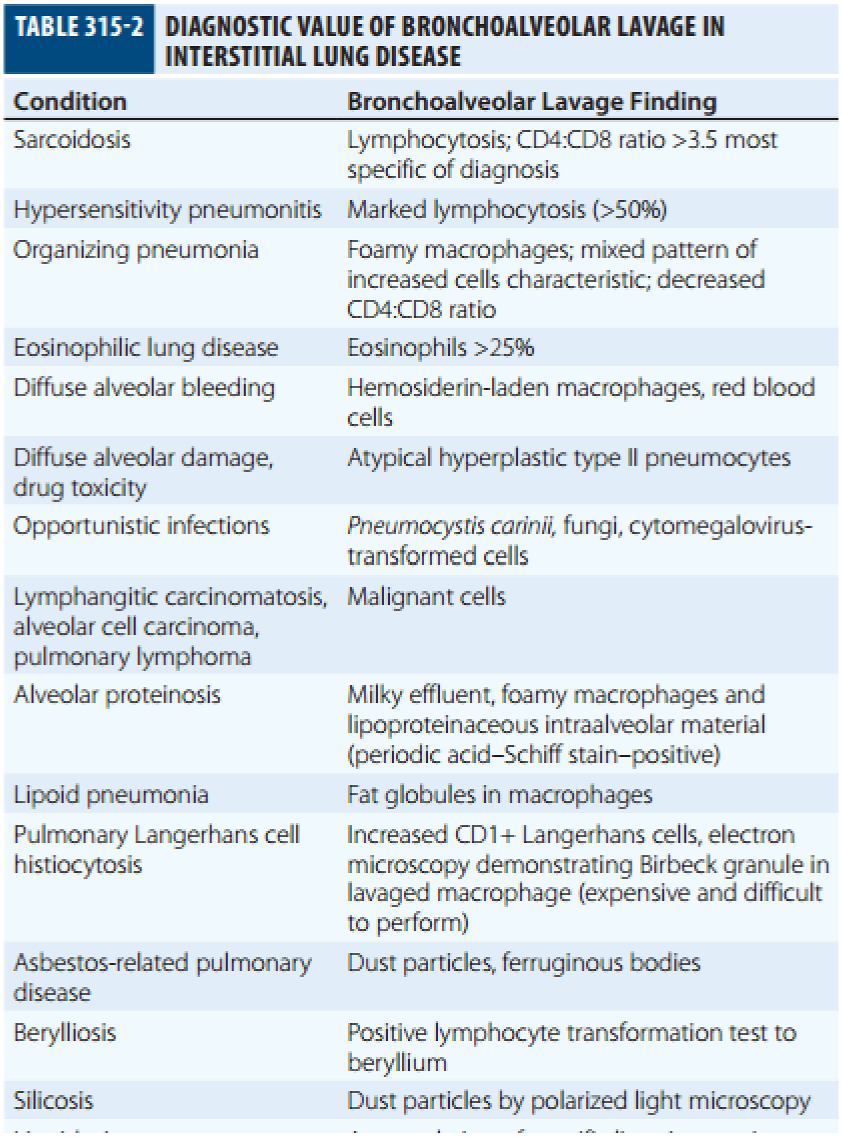


TABLE 315-2 **DIAGNOSTIC VALUE OF BRONCHOALVEOLAR LAVAGE IN INTERSTITIAL LUNG DISEASE**

Condition	Bronchoalveolar Lavage Finding
Sarcoidosis	Lymphocytosis; CD4:CD8 ratio >3.5 most specific of diagnosis
Hypersensitivity pneumonitis	Marked lymphocytosis (>50%)
Organizing pneumonia	Foamy macrophages; mixed pattern of increased cells characteristic; decreased CD4:CD8 ratio
Eosinophilic lung disease	Eosinophils >25%
Diffuse alveolar bleeding	Hemosiderin-laden macrophages, red blood cells
Diffuse alveolar damage, drug toxicity	Atypical hyperplastic type II pneumocytes
Opportunistic infections	*Pneumocystis carinii*, fungi, cytomegalovirus-transformed cells
Lymphangitic carcinomatosis, alveolar cell carcinoma, pulmonary lymphoma	Malignant cells
Alveolar proteinosis	Milky effluent, foamy macrophages and lipoproteinaceous intraalveolar material (periodic acid–Schiff stain–positive)
Lipoid pneumonia	Fat globules in macrophages
Pulmonary Langerhans cell histiocytosis	Increased CD1+ Langerhans cells, electron microscopy demonstrating Birbeck granule in lavaged macrophage (expensive and difficult to perform)
Asbestos-related pulmonary disease	Dust particles, ferruginous bodies
Berylliosis	Positive lymphocyte transformation test to beryllium
Silicosis	Dust particles by polarized light microscopy

ROLE OF LUNG BIOPSY

- When the results of the above evaluation do not allow the clinician to make a confident diagnosis of a given type or stage of interstitial lung disease (ILD), lung biopsy with multidisciplinary interpretation of the results may be necessary.
- Indications
  - atypical or progressive symptoms and signs (fever, weight loss, hemoptysis, signs of vasculitis)
  - atypical radiographic features
  - unexplained extrapulmonary manifestations
  - rapid clinical deterioration, or
  - sudden change in radiographic appearance.

Treatment of ILD

- Although the course of ILD is variable, progression is common and often insidious. **All treatable possibilities should be carefully considered.**
- Because therapy does not reverse fibrosis, the **major goals of treatment** are
  - permanent removal of the offending agent, when known, and
  - early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage.
- Hypoxemia ($PaO_2 < 55$ mmHg) at rest and/or with exercise should be managed with **supplemental oxygen.**
- **Management of cor pulmonale** may be required as the disease progresses.
- **Pulmonary rehabilitation** has been shown to improve the quality of life in patients with ILD.

DRUG THERAPY

- **Glucocorticoids**
  - **They** are the **mainstay of therapy for suppression of the inflammation** present in ILD, but the success rate is low.
  - there is no direct evidence that steroids improve survival in many of the diseases for which they are commonly used.
  - Glucocorticoid therapy is **recommended for symptomatic ILD patients** with eosinophilic pneumonias, COP, CTD, sarcoidosis, hypersensitivity pneumonitis, acute inorganic dust exposures, acute radiation pneumonitis, DAH, and drug-induced ILD.
  - In organic dust disease, glucocorticoids are recommended for both the acute and chronic stages.
  - The optimal dose and proper length of therapy with glucocorticoids in the treatment of most ILDs are not known.
  - A common starting dose is **prednisone**, **0.5 - 1 mg/kg**, PO, daily for 4—12 weeks, at which time the patient is reevaluated.
    - If the patient is stable or improved, the dose is tapered **to 0.25—0.5 mg/kg** and is maintained at this level for an additional **4—12 weeks**, depending on the course.
    - Rapid tapering or a shortened course of glucocorticoid treatment can result in recurrence.
    - If the patient's condition continues to decline on glucocorticoids, a second agent (see below) often is added and the prednisone dose is lowered to or maintained at **0.25 mg/kg** per day.
  - **Cyclophosphamide, azathioprine** (1 - 2 mg/kg/day), and mycophenolate mofetil, with or without glucocorticoids for 8—12 weeks
    - An objective response usually requires at least to occur.

    - In situations in which these drugs have failed or could not be tolerated, other agents, including methotrexate and cyclosporine, have been tried. However, their role in the treatment of ILDs remains to be determined.
- Many cases of ILD are chronic and irreversible despite the therapy discussed above, and **lung transplantation** may then be considered.

Chapter 3; TB/Tuberculosis/ (የሳንባ ነቀርሳ ፣ ቲቢ)

Dr. Mulualem. G, Dr. Asmare.W

Clinical features and how to write hx of TB patient

History

- **TB** Pt's may present with
    - **Pulmonary** TB symptoms
        - **Persistent cough for ≥ weeks**, (cough of any duration for HIV positives
        - **Fever for ≥ 2 weeks**
        - **Night sweats**
        - **Unexplained weight loss**
    - Extra pulmonary manifestations → Look at discussion section below
    - Both pulmonary and extrapulmonary
- **The most common symptom of pulmonary TB is a productive cough of ≥ 2 weeks**, which may be accompanied by other respiratory symptoms (SOB, chest pains, and hemoptysis) and/or **constitutional symptoms** (loss of appetite, weight loss, fever, night sweats, and fatigue).
- However, **cough might not be the predominant presentation** for certain population group, particularly in people living with **HIV, young children, and severely malnourished.** Hence, **high index of suspicion is required to diagnose** TB among these groups.
- **A history of contact** with infectious TB case, and presence of documented recent weight loss may indicate the presence of TB in such patients to warrant investigation.
- Some patients may present with;
    - Chest pains → due to pleurisy, muscle strain)
    - SOB (breathlessness) → due to extensive lung disease or concomitant pleural effusion
    - Localized wheeze → due to local Tuberculous bronchitis, or because of external pressure on the bronchus by an enlarged lymph node.

Characterization of patient history

- Cough (82%)
    - Gradual in onset → chronic (≥ 2 weeks)
    - Comes day and night without aggravating and relieving factor or worsen at night
    - Initially patients may present with dry cough
- Sputum
    - As said above Initially TB patients may present with dry cough, later becomes productive cough with
        - ✓ Mucoid (purulent) sputum
        - ✓ Non position dependent
        - ✓ Non blood tingled (sometimes blood streaked in cavitary lesions or haemoptysis /30%/)
        - ✓ Non foul smelling
        - ✓ ''X'' Arabic coffee cup per day
        - ✓ Increase in frequency and amount gradually
- B smx's
    - ✓ Fever (75%) → low grade, intermittent with/without chills and rigor
    - ✓ Night sweet (65%)
    - ✓ Weight loss (73%) → Significant weight loss (>5% of his/her initial body weight or significant but unquantified weight loss to the extent his/her cloth becomes loose)
- Appetite loss (61%)
- Easy fatigability

- SOB
    - ✓ Progressive in onset
    - ✓ Common if there is pleural effusion from disseminated TB
- Chest pain (pleuritic chest pain) /54%/ → also from pleural effusion and characterized by
    - ✓ Sudden, sharp, stabbing, localized pain
    - ✓ Aggravated by deep breathing, coughing, sneezing, laughing etc
    - ✓ Relieved by assuming to the same side of the effusion
        - ○ N.B pain relieved by leaning forward in pericarditis
    - ✓ May radiate to shoulder or back
    - ✓ Associated with rapid and shallow breathing, SOB, dry cough

☛ **Manifestations of HIV-infected patients →** Refer under RVI section of Nitsbin (click here →*RIV - TB*)

Risk factors

- Determinants of transmission
    - Duration of **contact with TB pt**
    - Shared environment of contact (e.g poorly ventilated house)
    - Similar illness in the family, living in the same house or dormitory, camp, refuge place
    - Geographical location → TB is common in 3rd world countries
- RF for developing disease after infection
    - Cigarette smoking
    - Comorbidities → RVI (RVI increase risk of acquiring TB, 20-37 times greater lifetime risk than HIV negative), DM, CKD…
    - Recent infection (< 1 year)
    - Fibrotic lung disease
    - Malnutrition and immunocompromisation
- LOC → increase risk of Aspiration
- Industrial chemical exposure

Complication of TB

- **Pulmonary complications of TB** include
    - Hemoptysis
    - Pneumothorax, bronchiectasis
        - TB is the commonest acquired cause of bronchiectasis in our set up (N.B Cystic fibrosis is the commonest cause of bronchiectasis in western set up)
    - Extensive pulmonary destruction
        - Post TB fibrosis which result in COPD
    - Malignancy and
    - Chronic pulmonary aspergillosis.
        - Aspergilloma formation in TB cavitary lesions → infection of cavity by aspergillus flavus
- Extra pulmonary TB
    - ✓ TB lymphadenitis
    - ✓ Genito urinary TB
    - ✓ Skeletal TB
    - ✓ Pleural TB which may complicate with Empyema formation
    - ✓ TB pericarditis
    - ✓ TB peritonitis
    - ✓ Intestinal TB

- ✓ TB meningitis and Tuberculoma
- ✓ Miliary TB

Sample history

Chief compliant

Cough of 3 weeks duration

HPI

This patient was last relatively healthy 03 weeks back at which time she started to experience a gradual onset of initially dry cough which Comes day and night without aggravating and relieving factor. Later becomes non position dependent productive cough with Mucoid, non-position dependent, Non blood tingled, non-foul-smelling sputum of half to 1 Arabic coffee cup per day which Increase in frequency and amount progressively. Associated with this she also experienced low grade, intermittent fever, profuse night sweat to the extent her under wear becomes soaked and unquantified but significant weight loss to the extent her clothes become loose but no SOB or chest pain.

- 10 years back, her husband was diagnosed with Pulmonary TB. Diagnosis was made with sputum examination and CXR at addis zemen primary hospital. He discontinued the medication due to unknown reason and died *(contact hx is strong RF)*
- Currently she is not married and lives in family size of 4. She has 3 boys and one daughter. All are above 5 years old, alive and healthy. *(family screening, especially those under five years old, is one of principle of management)*
- Lives in well ventilated iron corrugated house having 2 windows and one door, all are functional, with separate kitchen. (poorly ventilated house accelerates TB transmission and RF for COPD → DDX)
- She was screened for RVI 04 months back and found to be NR (RVI increase risk of acquiring TB 37x than seronegative persons)
- No hx of Cigarette smoking, or hemoptysis (cigarette is RF for developing disease after TB infection, and RF for Lung ca → DDX)
- No hx of abnormal body movement, LOC or tracheal intubation (aspiration → RF)
- No hx of DM, HTN or Asthma (comorbidities → RF)
- No hx of swelling over the neck, axilla or groin (LN TB or scrofula → CXN)
- No hx of Flank pain, dysuria, urgency, frequency or hematuria (Genito urinary TB /stricture, pyelonephritis, sterile pyuria…. Infertility and menstrual abnormality in females/ → cxn)
- No hx of bone pain, joint pain or swelling (bone TB → CXN)
- No hx of tinnitus, blurring of vision, light headedness or easy fatigability (anaemia 2ry to bone marrow suppression _ bone TB → CXN)
- No hx of headache, fever or neck stiffness (TB meningitis → CXN)
- No hx of back pain, body weakness or back bone deformity (gibbus formation which result in paraplegia → CXN)

- No hx of bone pain, herbicide exposure, epistaxis or bleeding from other body sites *(mediastinal lymphoma → DDX)*
- No hx of dyspnea, leg swelling or RUQ abdominal pain *(COPD and Cor pulmonale → DDX. N.B considering COPD as DDX with this short duration of cough in this case, makes very unlikely)*
- No hx of tooth extraction, lower facial pain or nasal discharge (RF for lung abscess → DDX)
- No hx of drug intake *(DDX for coughing)*
- No hx of contact with animal abortus material *(even though extremely rare, brucellosis can present as TB → DDX)*

Finally, she was admitted to our hospital supported physically by her families

Physical examination (pertinent findings)

1 GA → Chronically sick looking

2 Vital signs

- Febrile → TB is one of the causes of FUO (fever of unknown origin)
- Tachycardia and tachypnoea → especially in miliary TB
- Low BMI → emaciated (Cachexia)

3 HEENT

- Pale conjunctiva → Anaemia from skeletal TB with bone marrow involvement

4 LGS

- Cervical or supraclavicular LAP → TB lymphadenitis

5 RS

- Clubbing
- Signs of pleural effusion
- Rales, rhonchi, amphoric breath sound
- Apical consolidation signs
- Localized wheeze → TB bronchitis, LAP obstructing the bronchus

6 CVS

- Pericardial friction rub → TB pericarditis

7 Abdominal examination

- Tiped splenomegaly with/without hepatomegaly → Miliary TB
- Palpable mass and intestinal obstruction → intestinal TB
- Huge Ascites → TB peritonitis
- GOO (Gastric outlet obstruction) → TB LAP obstructing the pylorus

8 GUS → CVAT from genitourinary TB

9 MSS

- Back bone tenderness and deformity → gibbus (TB spondylitis)
- Knee swelling (bone and joint TB)

10 IS

- Palmar pallor → Anaemia from skeletal TB with bone marrow involvement
- Erythema nodosum commonly in shins and rarely in thigh → primary TB

11 NS

- Meningeal irritation signs → TB meningitis
- Paraplegia → pott's disease

DDX for patients presenting with chronic cough

1) Pulmonary TB
2) Lymphoma
    - Present with B smx's as the same as TB (fever, night sweat, weight loss)
    - **Mediastinal lymphoma (NHL)**
        - ✓ Misdiagnosed as TB

☛ *Case scenario; One Patient with mediastinal lymphoma at UOG Hospital, was misdiagnosed as pulmonary TB and she was on anti TB for a long period of time but no improvement. Finally, mediastinal lymphoma was diagnosed after chest CT scan was done (ward c, @2012 e.c.)*

3) Cor pulmonale
4) COPD
5) Bronchiectasis
6) Lung abscess → very offensive foul-smelling sputum and fever is typical for lung abscess
7) ILD
    - Pt's present with prolonged unexplained SOB, dry cough
    - Misdiagnosed as TB

For Cor pulmonale, COPD, Bronchiectasis, Lung abscess and ILD refer chapter 2 (click here → Chapter 2; Cor pulmonale and Chronic lung disorders

Chapter 2;)

8) Lung ca
    - **usually have +ve family hx of lung ca, common in smokers and present with bloody sputum.**
    - refer under long case of nitsbin (click here → Chapter 4; Lung cancer (የሳንባ ካንሰር))
9) SLE

- F: M ratio is 9:1
- Involves lung, pleura (pleural effusion), pericardium (leg edema)
- refer under short case of nitsbin (click here →Systemic lupus erythematosus (SLE) (lupus))

10) MAC (mycobacterium avium complex)
11) FUNGAL infections
12) GERD
13) VL
14) Brucellosis
    - ✓ Extremely rare
    - ✓ associated with animal abortus exposure
    - ✓ caused by brucella abortus
    - ✓ have similar clinical picture as TB and difficult to differentiate

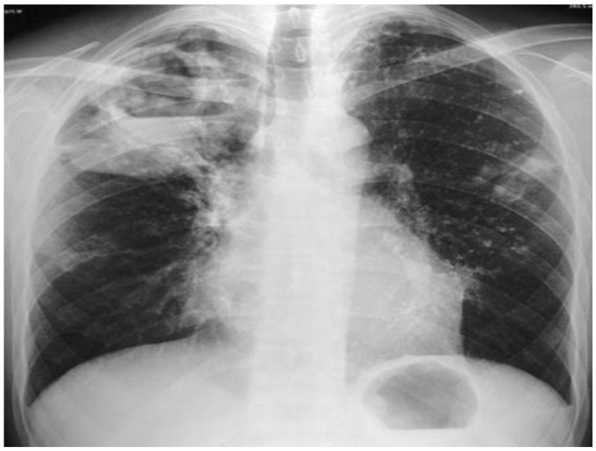
For RVI - TB DDX refer under RVI of Nitsbin (click here →

Pneumonia with parapneumonic effusion

IX

A. Diagnosis For active TB

1. **CXR** → what do you expect from CXR?
    - There is no pathognomonic sign
    - Upper lobe lesion with or without cavity (**reactivation TB**)
    - Apical consolidation
    - Lower lobe opacity, hilar, peritracheal or mediastinal lymphadenopathy (**primary TB**)
    - Hilar LAP (post primary TB)
    - Milliary pattern may be helpful in diagnosing some forms of extrapulmonary TB
    - Normal in 30% of HIV pts. With TB
    - Pleural effusion → request PA and lateral decubitus view CXR if you suspect pleural effusion
        - ✓ Obliterated costophrenic angle
        - ✓ +ve meniscus sign
        - ✓ Haziness over the dependent lung field
    - Old granuloma
    - Infiltration



Picture; **CXR showing a right-upper-lobe infiltrate** and a **cavity with an air-fluid level** in a patient with **active tuberculosis**

2. **Sputum examination**

- Sputum examination includes
    - AFB microscopy
    - Culture → gold standard, minimum of 10-100 bacilli per ml are required for growth, unlike AFB microscopy which needs approximately 10,000 bacilli per ml for detection of bacteria
    - Gene expert → TB dx, RMP sensitivity
    - Gram stain → to screen bacterial superinfection
    - PCR if available
- **AFB microscopy**
    - The detection of acid-fast bacilli (AFB) on microscopic examination of stained sputum smears is the most rapid and inexpensive TB diagnostic tool.
    - A serious of **at least 3 single specimens** should be **collected in 8 to 24 hours interval** (with **at least one** specimen obtained **early in the morning**) which should be submitted to the laboratory for AFB smear and mycobacterial culture, although the **diagnosis often can be made with 2 specimens**
        - **Spot - morning - spot examination (currently we are using spot - spot examination only)**
    - If pt present with dry cough, use induced sputum with BAL or hypertonic saline method
    - Sputum AFB smears are relatively **less sensitive (45 - 80%)** than nucleic acid amplification (NAA) or culture; **approximately 10,000 bacilli per mL are needed for detection of bacteria** in AFB smear using light microscopy.

- MYCOBACTERIAL CULTURE
    - **+ve in 80%** of active TB
    - **Gold standard**, minimum of 10-100 bacilli per ml are required for growth
    - *6 - 8 weeks may be required before growth* is detected for conventional media and 1-3wks for Liquid media

        - 1-2 wks more for sensitivity test
    - **Gene x-pert** (*Nucleic acid amplification technology)*
        - Useful in the **diagnosis of AFB-negative pulmonary and extrapulmonary TB.**
        - Detects **Rifampicin resistance**
        - **Have Sensitivity of 98%** among **AFB-positive** cases and **~70% among AFB-negative** specimens
        - Results available in 4-6 hours

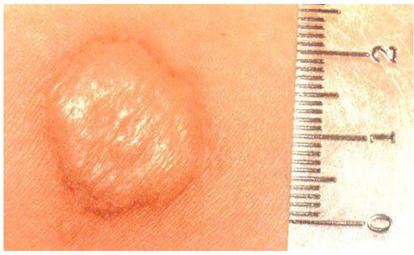
N.B

- Smear +ve TB
    - 2 +ve sputum examination or
    - 1 +ve sputum examination and one of the following
        - 1 culture +ve examination or
        - Typical CXR finding or
        - RVI pt
- Smear -ve TB
    - Culture +ve but doesn't fulfil the above criteria and unresponsive to broad spectrum antibiotics
        - ✓ For smear -ve patients
            - Repeat smear and request CXR
            - If all IX including CXR do not suggest TB, prescribe antibiotics for two weeks
- Follow up sputum examination (Look at management part below)
    - Sputum examination for all new smear +ve pt's should be repeated at 2nd, 5th, and 6th months
    - Sputum examination for previously treated patient should be done at 3rd, 5th and 8th months

3. **Pleural fluid analysis** → for pleural involvement; refer under short cases of nitsbin (click here → pleural fluid analysis)
    - Determinations of ADA and IFN-γ levels in pleural fluid may be useful adjunctive tests in the diagnosis of pleural TB (**Tuberculous pleural effusion is a value >40 U/L**).

B. DIAGNOSIS OF LATENT M. TUBERCULOSIS INFECTION (LTBI)

4. **TST/Tuberculin skin test/ (Mantoux test) → PPD** (purified protein derivative) a.k.a Tuberculin
    - The **Mantoux TST** is the intradermal injection of 0.1 ml purified protein derivative (PPD). For Indurations, measure after 48-72hrs
    - Tuberculin sensitivity develops 3 weeks to 3 months (most often in 4-8 weeks) after inhalation of organisms



Picture; TST induration

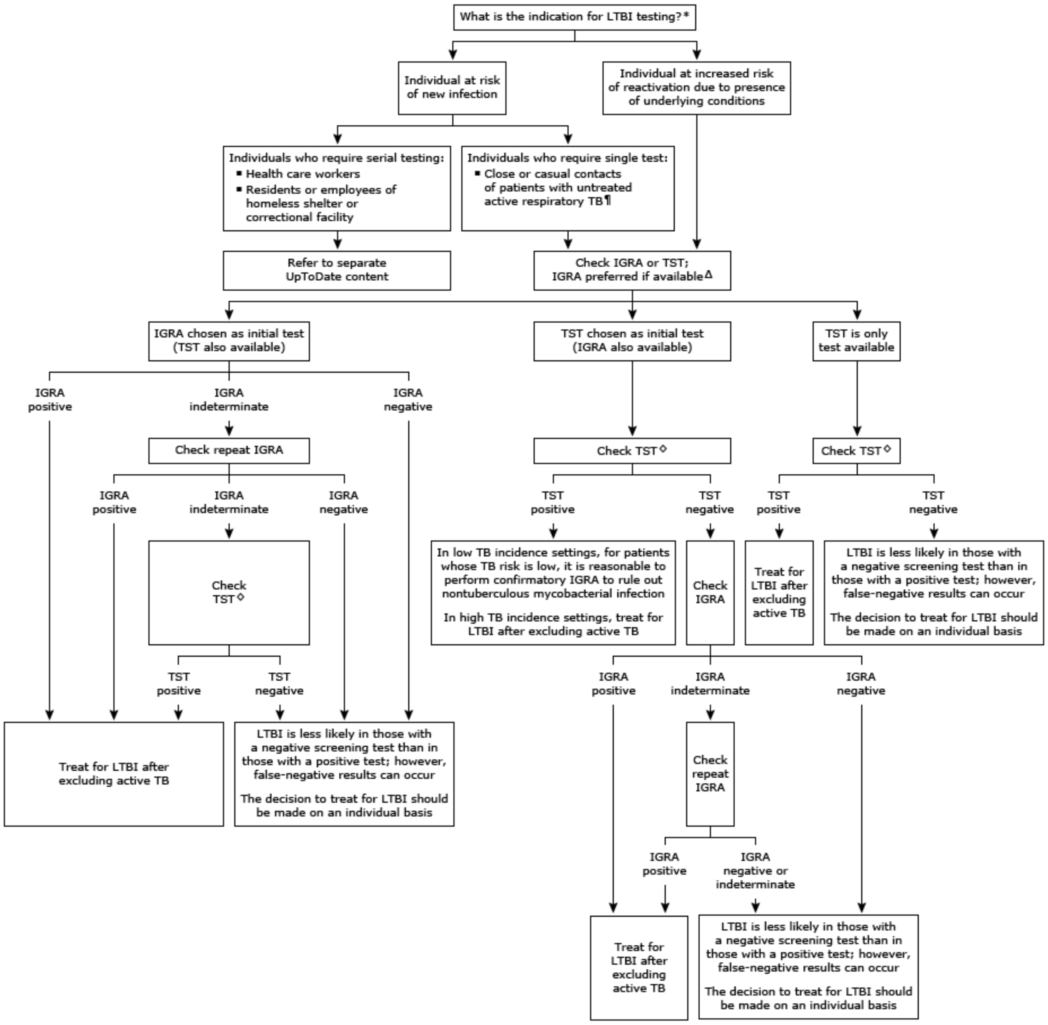
A TST should be regarded as positive in the following circumstances:

- **PPD ≥ 5mm** within 48-72hrs suggest +ve test in the following conditions
  - **For immunocompromised patients** (like RVI &organ transplant pts) because they have less reactive immunity
  - Recent contact of TB patient
  - Fibrotic changes on CXR suggestive of old TB
  - Patients on treatment with TNF-alpha blockers
- **PPD ≥ 10mm induration**
  - Recent arrivals from high prevalence countries
  - Injection Drug Users
  - Nursing Homes, Prisons
  - Mycobacterial Lab. Workers
- PPD ≥ 15mm is a +ve test even if the is no risk factor for TB
- Extremely important for children (for those not vaccinated with BCG) and latent TB in adult
- **False negative PPD test**
  - Overwhelming TB
  - Wrong techniques
  - Immunocompromised patients
    - HIV
    - Steroids
    - Cancer
    - Measles and
    - Severe PEM (Protein energy malnutrition) i.e. SAM in children
- **False positive PPD test**
  - Atypical mycobacterial infections
  - Hypersensitivity to constituents
  - BCG vaccination

5. IGRA (interferon-gamma release assay)

- Both TST and IGRA are recommended for immunocompromised adults (although intended to increase sensitivity in this high-risk group, there is no specific evidence to support this practice); LTBI treatment is warranted if either test is positive. Immunocompromised children should be referred to a specialist.

- TST is recommended for new entrants from high-incidence countries who present to health care services; an IGRA can be offered if TST not available.
- IGRA alone may be used for outbreak situations and other circumstances in which follow-up for TST interpretation may be difficult.


What is the indication for LTBI testing?*
Individual at risk of new infection
Individual at increased risk of reactivation due to presence of underlying conditions
Individuals who require serial testing:
▪ Health care workers
▪ Residents or employees of homeless shelter or correctional facility
Individuals who require single test:
▪ Close or casual contacts of patients with untreated active respiratory TB¶
Refer to separate UpToDate content
Check IGRA or TST; IGRA preferred if availableΔ
IGRA chosen as initial test (TST also available)
TST chosen as initial test (IGRA also available)
TST is only test available
IGRA positive
IGRA indeterminate
IGRA negative
Check repeat IGRA
IGRA positive
IGRA indeterminate
IGRA negative
Check TST◊
TST positive
TST negative
Treat for LTBI after excluding active TB
LTBI is less likely in those with a negative screening test than in those with a positive test; however, false-negative results can occur
The decision to treat for LTBI should be made on an individual basis
Check TST◊
TST positive
TST negative
In low TB incidence settings, for patients whose TB risk is low, it is reasonable to perform confirmatory IGRA to rule out nontuberculous mycobacterial infection
In high TB incidence settings, treat for LTBI after excluding active TB
Check IGRA
Check TST◊
TST positive
TST negative
Treat for LTBI after excluding active TB
LTBI is less likely in those with a negative screening test than in those with a positive test; however, false-negative results can occur
The decision to treat for LTBI should be made on an individual basis
IGRA positive
IGRA indeterminate
IGRA negative
Check repeat IGRA
IGRA positive
IGRA negative or indeterminate
Treat for LTBI after excluding active TB
LTBI is less likely in those with a negative screening test than in those with a positive test; however, false-negative results can occur
The decision to treat for LTBI should be made on an individual basis

C. Baseline investigation

6. **CBC**
   - NcNc anaemia
   - Thrombocytopenia 2ry to Rifampicin treatment
7. **ESR** → elevated (supportive for diagnosis)
8. **U/A** → U/A done as baseline, urine culture may be done for dx
   - Sterile pyuria (i.e. culture -ve pus in urine)
   - Urine culture may be +ve for genitourinary TB
9. **RFT** → as a Pre-treatment Evaluation

- BUN and creatinine to start ant TB treatment, since anti TB drugs have nephrotoxic effect (e.g. streptomycin is nephrotoxic)

10. **LFT** → as a Pre-treatment Evaluation, anti TB drugs have hepatotoxic effect (especially pyrazinamide)
11. **PICT** → RVI -TB coinfection is very common
12. **Urine HCG** → for all women of child bearing age, as a Pre-treatment Evaluation

D. Additional investigations to be done based on indication

- For patients with suspected, any form of, extrapulmonary TB.
    - BAL (Bronchoalveolar lavage), Fiberoptic bronchoscopy
        - Invasive diagnostic procedures
        - Then, AFB, Gene expert, culture, gram stain can be done from the sample
- For extra pulmonary TB involving the pleura
    - **Pleural fluid analysis is the common investigation in our set up**
    - **CXR**
    - Chest U/S
        - Can differentiate
            - Loculated effusion from tumour
            - Pleural effusion from thickening of pleura
        - Guide thoracentesis
    - Chest CT scan and MRI
    - **Pleural biopsy**
        - Diagnostic for pleural TB
        - Granuloma formation is expected
        - Culture +ve in 80% Of Cases

- TB lymphadenitis
    - FNAC, LN Biopsy, AFB, Tissue culture (50%+ve)
    - From enlarged LN
    - N.B Biopsy also can be taken from pleura and solid lesions
- TB peritonitis
    - Abdominal U/S
    - Peritoneal TAP
- Musculo skeletal tuberculosis (TB)
    - X-ray of the involved part
    - Synovial fluid aspiration or synovial biopsy and analysis if there is Joint swelling
        - findings of Synovial fluid analysis are usually nonspecific
    - Microscopy and culture of infected material
        - Tissue may be obtained by needle aspiration and/or biopsy; CT guidance is useful in regions where available.
    - CT or MRI reveals the characteristic lesion.

  - But, consider if other IX failed to suggest DX (this is for cost effectiveness)

- TB Pericarditis
  - Echo, CT, or MRI → shows effusion and thickness across the pericardial space.
  - Pericardiocentesis under echo guidance
    - exudative fluid, with a high count of predominantly lymphocytes and monocytes
    - hemorrhagic effusion is common.
  - Direct smear examination → is very rarely positive.
  - Culture → +ve in up to 2/3rd of cases
    - pericardial biopsy has a higher yield.
- Intracranial TB
  - MRI is useful in the diagnosis of intracranial TB
  - Tuberculous meningitis
    - ✓ LP (CSF analysis)
  - Tuberculoma
    - ✓ Brain MRI/CT
    - ✓ For intracranial TB like tuberculoma (biopsy is necessary to dx tuberculoma)
- For Genito urinary TB
  - Diagnosis requires biopsy or culture of specimens obtained by dilation and curettage.
    - Culture -yields a definitive diagnosis in nearly 90% of cases.
    - Culture-negative pyuria in acidic urine should raise the suspicion of TB (i.e. Pyuria in U/A but culture -ve, which is known as sterile pyuria)
- Hydronephrosis
  - IV pyelography
  - Abdominal U/S
  - Abdominal CT/MRI
- Stricture secondary to Genito urinary TB
  - Cystourethrography can show;
    - Deformities and obstructions, calcifications and ureteral stricture
  - CT and MRI are more sensitive if Cystourethrography fails to detect

Discussion

3.1 Pulmonary TB

1. Definition of terminologies in TB infection

- **Pulmonary TB (PTB) → M. Tuberculosis infection localized to lung parenchyma or the tracheobronchial tree**

- **Extra pulmonary TB → lymphohematogenous spread or local extension of M. Tuberculosis to different organ systems**. It includes disseminated and miliary patterns of dissemination. E.g. Disseminated TB to the lungs, pleura and peritoneum
- **Disseminated TB** → a mycobacterial infection in which mycobacteria have **spread** from the lungs to other parts of the body through the **blood or lymph system**.
- **Miliary tuberculosis** → used to denote all forms of progressive, widely disseminated **hematogenous** TB which spreads to various organs. some authors use disseminated TB interchangeably with miliary TB. however, **miliary TB** in fact **refers more specifically to disseminated TB which presents with a millet-seed-like appearance on a chest x ray**, when the disease is spread by blood throughout the lungs. **Miliary TB is classified as PTB because there are lesions in the lungs** (look at miliary TB section below)

E. EPIDEMIOLOGY

- ***Mycobacterium tuberculosis*** **is the second most common infectious cause of death in adults worldwide** (second to HIV, which is the most common infectious cause of death).
- The human host serves as a natural reservoir for *M. tuberculosis*
- More than two billion people (about 30 percent of the world population) are estimated to be infected with *M. tuberculosis*. The global incidence of tuberculosis (TB) peaked around 2003 and appears to be declining slowly.
- The epidemiology of TB varies substantially around the world. The highest rates are observed in sub-Saharan Africa, India, and the islands of Southeast Asia and Micronesia.

Tuberculosis situations in Ethiopia

- Tuberculosis is a major public health problem posing significant deleterious health impacts by affecting the productive segment of the population and resulting serious burden to the health system and exploiting the individuals/household economy.
- Ethiopia remains to be among the 30 countries reported with high burden of TB, TB/HIV and DR-TB for 2015 to 2020.
- TB related mortality is highlighted in the top 10 reported causes of death among hospital admissions, with annual estimated death rate of 26 per 100,000 populations in 2015

F. Microbiology, Natural history, and pathogenesis

MICROBIOLOGY

- *M. tuberculosis* belongs to the genus *Mycobacterium*, which includes more than 50 other species, often collectively referred to as nontuberculous mycobacteria.
- Tuberculosis (TB) is defined as a disease caused by members of the *M. tuberculosis* complex, which include the tubercle bacillus (*M. tuberculosis*), *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*, *M. caprae*, *M. pinnipedii,* and *M. orygis*

Transmission of *M. tuberculosis*

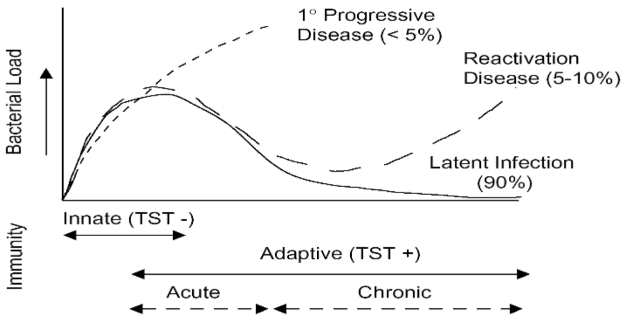
- From inhalation of droplet nuclei (1-5 *u*m in diameter) produced when patient with pulmonary or laryngeal TB coughs. Rarely from ingestion of raw milk from cows affected by bovine TB, congenital
- Transmission facilitated by prolonged exposure to infectious environment; small enclosed spaces with inadequate ventilation
- **The probability of transmission depends on the dynamics of four major factors**:
- ✓ The susceptibility of the host
- ✓ Degree of infectiousness of the person with TB disease
- ✓ Environmental factors and
- ✓ Level of exposure (proximity, frequency and duration).
- The risk of infection of a susceptible individual is therefore higher with **close**, **prolonged**, **indoor exposure** to a person with infectious pulmonary TB.
- **Patients with cough who are AFB smear +ve are considered most infectious**
- **The most infectious patients have cavitary pulmonary disease or laryngeal TB or endobronchial TB.**
- Sputum smear-negative/culture positive TB patients are less infectious, responsible for < 20% of transmission.
- Culture negative pulmonary TB and Extrapulmonary TB pts are generally non-infectious.
- Persons with both HIV infection and TB are less likely to have cavitation's, they may be less infectious than persons without HIV co-infection.
- Population groups with conditions that **compromise the immune system**, including People living with **HIV, Diabetics, young age** groups and **malnourished, are at higher risk of developing Active TB** as they fail to contain the latent TB infection from progressing to active disease.
- Besides, **congregated settings like prisons, refugee camps, homeless shelters and urban slums** are usually overcrowded and poorly ventilated. The inhabitants usually are very poor, neglected and marginalized contributing to **higher transmission risk and susceptibility to TB**.
- Consumption of raw milk containing M.bovis is also a possible way of getting infected by TB, though it is much less frequent.

Natural History of *M. tuberculosis* Infection

- Inhalation of aerosol droplets containing *M. tuberculosis* with subsequent deposition in the lungs leads to one of four possible outcomes:
    1. **Immediate clearance of the organism**
    2. **Primary disease:** immediate onset of active disease (**common among children, not associated with high-level transmissibility, middle and lower lung zones)**
    3. **Latent infection**
    4. **Reactivation disease:** onset of active disease many years following a period of latent infection (**frequently cavitary and more often infectious**

than primary disease, usually localized to the apical and posterior segments of the upper lobes)

- In the great majority (90-95%) of persons infected with M. Tuberculosis, the immune system either kills the bacilli or perhaps more often, keeps them suppressed (silent focus) resulting in a latent TB infection (LTBI).
- In immunocompetent individuals, only 5-10% of infected persons develop active disease in their lifetime.
- Individuals with latent TB infection do not have symptoms as there is no tissue destruction by the bacilli and are not infectious.
- Active TB disease may arise from progression of the primary lesion after infection, or from endogenous reactivation of latent foci, which remained dormant since the initial infection, or from exogenous re-infection.
- The progression from LTBI to TB disease may occur at any time, from soon to many years later.
- Post primary TB usually affects the lungs though any body part can be affected after haematogenous and/or lymphatic spread of the bacilli.
- Persons who have Active TB are usually infectious
- **Natural history of confirmed TB disease (without HIV) if left untreated**
    - **50% die in 5 year**
    - **25% cured**
    - **25 % chronically positive (infectious)**



CLINICAL MANIFESTATION

Presumptive Tuberculosis case;

- Any person who presents with symptoms and/or signs suggestive of tuberculosis, in particular **cough of ≥ 2 weeks duration,** which may be accompanied by **other respiratory symptoms** (shortness of breath, chest pains, and hemoptysis) **and/or constitutional symptoms** (loss of appetite, weight loss, fever, night sweats, and fatigue).
- Presumptive TB case also includes any person with **CXR abnormality suggestive of TB** with or without other symptoms/signs suggestive of TB.

Case of tuberculosis:

- Refers to a patient in whom TB has been **bacteriologically Confirmed or diagnosed by a clinician decision.**

A bacteriologically confirmed TB case:

- Refers to a patient from whom **at least one biological specimen is positive** mycobacterium TB by either smear microscopy, Xpert MTB/RIF, culture or other WHO approved bacteriologic detection tests.

A clinically diagnosed TB case:

- A patient who **does not fulfil** the criteria for a **bacteriological confirmed case** but, has been **diagnosed** with active TB by an **experienced clinician** and is decided to be given, a full course of TB treatment.
- This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases diagnosed without confirmation of mycobacterium TB.

3.2 Extra Pulmonary TB

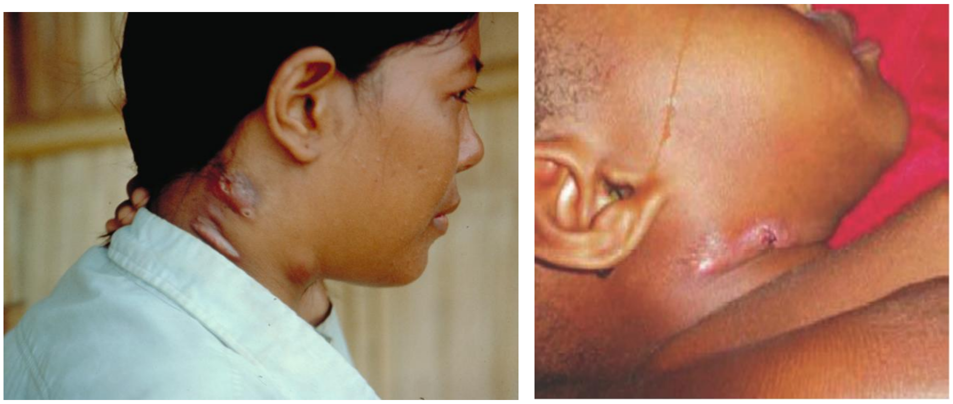
CLASSIFICATIONS → pulmonary, Extrapulmonary or both.

- Extrapulmonary TB may occur in 10-40% of patients.
- Patients may present with non-specific symptoms such as unintentional weight loss, night sweats and fever for more than 2 weeks. Other symptoms depend on the site or organ affected.
- Commonly involved sites are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium.
- Extra pulmonary TB is seen commonly due to HIV
  - ✓ Up to 2/3rd of HIV infected patients with TB may have both pulmonary and extrapulmonary or extrapulmonary TB alone.

1. TB LYMPHADENITIS

- ✓ The **most common** presentation of **extra pulmonary TB**
- ✓ **Common in children** and in person with **advanced stages of HIV** infection.
- ✓ **Cervical Lymph nodes** is the **commonest sites** of involvement, though axillary and intraabdominal lymph nodes may also be affected. Most commonly ***at posterior cervical and supraclavicular sites.***
- ✓ Slowly developing painless swelling on the sides of the neck is the commonest complaint.
- ✓ **Initially cervical lymph nodes are firm and discrete**, and may **later** and may later be **matted together** and become **fluctuant**
- ✓ The overlying skin may breakdown with the formation of abscesses and chronic **discharging sinuses /scrofula/,** which heal with scarring.
- ✓ In HIV infected patients, lymphadenopathies can be acute and resemble acute pyogenic lymphadenitis.
- ✓ be matted, non-tender LN, sinus drainage/scrofula/, Painless swelling of the lymph nodes.

- ✓ 50% of cases have pulmonary involvement, systemic symptoms are uncommon except in HIV-infected patients.
- ✓ **DX → FNAC, Biopsy, AFB, Tissue culture (50%+ve)**



Pictures; TB lymphadenitis with a draining sinus tract /scrofula/

2. Tuberculous pleural effusion

- ➢ TB is the commonest cause of a unilateral pleural effusion. It is also the commonest form of HIV-related extra-pulmonary disease
- ➢ Most often present as **non-productive cough of acute onset**, **chest pain, SOB and Fever**.
- ➢ Isolated pleural effusion usually reflects recent primary infection, and the collection due to hypersensitivity response to mycobacterial antigens or Contiguous parenchymal spread.
- ➢ The effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea.
- ➢ Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds.
- ➢ **DX;**
  - ✓ **CXR-** effusion, may show parenchymal lesion
  - ✓ **Thoracentesis-** straw colored and at times hemorrhagic fluid, Exudative → refer short case of Nitsbin (click here → pleural fluid analysis)
  - ✓ **AFB smear, and cultures** often negative
  - ✓ Pleural concentration of adenosine deaminase (**ADA > 40 U/L**) and **IFN-γ**
  - ✓ **Xpert MTB/RIF-** 75% +ve
  - ✓ **Pleural Biopsy**: granulomas and/or yields a positive culture in 80%.

3. Tuberculous empyema

- It is a less common complication of pulmonary TB; from rupture of a cavity or a bronchopleural fistula.
- **CXR** shows hydro pneumothorax with an air-fluid level.
- The pleural fluid is purulent and thick and contains large numbers of lymphocytes.
- Acid-fast smears and mycobacterial cultures are often positive.
- Surgical drainage is usually required as an adjunct to chemotherapy.

- Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease.
- Removal of the thickened visceral pleura (*decortication) is occasionally necessary to improve* lung function.

4. TB of CNS

- TB meningitis and intracranial tuberculoma are the two most common forms.

4.1 TB MENINGITIS

- ~5% of extrapulmonary cases
- Results from the hematogenous spread of primary or post primary pulmonary TB or from the rupture of a subependymal tubercle into the subarachnoid space.
- TB Meningitis is mainly a disease of childhood and young adults in developing countries.
- Develops in adults, especially those infected with HIV.
- It usually evolves over 2 to 6 weeks.
- Clinical manifestation includes;
  - Focal neurological deficits
  - Features of raised ICP
  - Signs of meningeal irritation
  - Focal or generalized seizures and
  - Cranial nerve palsies, the sixth nerve involvement being the most common.
- Presents subtly as **headache** and **slight mental changes** after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability.
- If not recognized, tuberculous meningitis may evolve acutely with **severe headache**, **confusion, lethargy, altered sensorium, and neck rigidity**
- Typically, the disease evolves over 1 - 2 weeks.
- **TB meningitis have 3 stages**
  - Stage I: **prodromal phase** → non-specific symptoms (fever, headache, confusion), no meningeal signs
  - Stage II: **meningitis phase** → typical disease with meningeal signs
  - Stage III: **comatose phase**

Diagnosis

- *Lumbar puncture is the cornerstone of diagnosis*
  - Examination of CSF → refer short case of Nitsbin (click here → CSF analysis)
  - Repeated lumbar punctures increase the yield
  - Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard
  - Xpert MTB/RIF has a sensitivity of up to 80% and is the preferred initial diagnostic option.

- Imaging studies (CT and MRI) → hydrocephalus and abnormal enhancement of basal cisterns or ependyma.
- If unrecognized, tuberculous meningitis is uniformly fatal.

- Neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed.

4.2 TUBERCULOMA

- Tuberculoma is an uncommon manifestation of CNS TB, presents as one or more space-occupying lesions.
- Intracranial tuberculoma can be asymptomatic or produce headache, seizure or some type of neurological impairment.
- On brain imaging, solitary tuberculoma (size: few mm to 3-4 cm) are more frequent than multiple lesions. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

5. GI TB

- Mechanisms are involved: swallowing of sputum, hematogenous spread, or (largely in developing areas) ingestion of raw milk from cows affected by bovine TB
- **The terminal ileum** and **the cecum** are the sites most commonly involved
- **Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation.**
- **Fever, weight loss, anorexia, and night sweats** are also common.
- **Tuberculous peritonitis** follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs (e.g. genital TB in women) or hematogenous seeding.
- Nonspecific abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis.
- Tuberculous peritonitis- paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutrophils occasionally predominate).
- The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis.

6. TB of the Upper Airways

- Nearly always a complication of advanced cavitary pulmonary TB.
- TB of the upper air ways may involve the larynx, pharynx, and epiglottis.
- Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough
- Acid-fast smear of the sputum is often positive
- Carcinoma of the larynx may have similar features but is usually painless.

7. Genitourinary TB Genitourinary TB

- Accounts for ~10—15%of all extrapulmonary cases.
- Involve any portion of the genitourinary tract.
- Local symptoms predominate

- ✓ Up to 75% of patients have chest radiographic abnormalities
- ✓ Urinary frequency, dysuria, nocturia, hematuria, and flank or Abdominal pain are common presentations.
- ✓ Asymptomatic and their disease discovered only after severe destructive lesions of the kidneys have developed.
- ✓ Urinalysis - in 90% of cases pyuria and hematuria.
- ✓ **Culture-negative pyuria** in acidic urine should raise the suspicion of TB

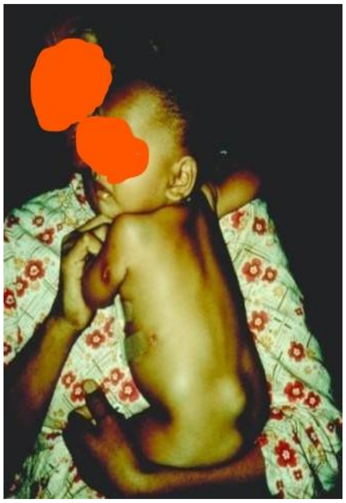
- ➢ **CT, MRI show;** deformities and obstructions, calcifications and ureteral stricture
- ➢ **Culture** -yields a definitive diagnosis in nearly 90% of cases.
- ➢ In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities.
- ➢ Diagnosis requires **biopsy or culture of specimens obtained by dilation and curettage.**
- ➢ In male patients, genital TB preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop.
- ➢ In almost half of cases of genitourinary TB, urinary tract disease is also present.
- ➢ Genitourinary TB responds well to chemotherapy.

8. SKELETAL TB

- ~10% of extrapulmonary cases
- Reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes
- TB can affect any bone but most commonly affects the vertebral column.
- Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected
- Active tuberculosis (TB) disease can develop immediately or after decades of latent infection.
- In highly endemic regions, musculoskeletal TB usually manifests clinically in the year following primary lung infection and therefore occurs most frequently in relatively young patients.
- Outside endemic areas, musculoskeletal TB is more commonly associated with late reactivation of infection and occurs mainly in adults.
- Two types of bone and joint involvement associated with TB infection have been described:
    - ○ **The caseous exudative type** → characterized by bone destruction, local swelling, abscess formation, sinus formation, and constitutional symptoms; it occurs most often in children.
    - ○ **The granular type** → more insidious and less destructive than the caseous exudative type, and abscess formation is less common; it occurs most often in adults. However, host-parasite interactions in tuberculosis are dynamic, often with mixed patterns and transitions along a continuum.
- Forms of skeletal tuberculosis (TB) include **spondylitis (Pott's disease**), **arthritis,** and **osteomyelitis.**

Tuberculous spondylitis (Pott's disease)

- Most commonly affects the **lower thoracic** and **upper lumbar region**; disease involving the cervical and upper thoracic region is less common.
- Infection generally begins with inflammation of the anterior aspect of the intervertebral joints; typically, it spreads behind the anterior ligament to involve the adjacent vertebral body. Once two adjacent vertebrae are involved, infection enters the adjoining intervertebral disc space.
- This tends to occur later in Pott's disease than in bacterial vertebral osteomyelitis and may have the radiographic appearance of relative disc sparing.
- Eventually, the avascular disc tissue dies; there is vertebral narrowing and subsequent vertebral collapse. **Gibbus deformity**, a form of structural kyphosis, distorts spinal canal anatomy. The spinal cord is then at risk of compression, resulting in paraplegia.



Picture; Gibbus deformity in an infant

- Spread may occur into the soft paravertebral tissue to form a so-called **"cold abscess"** (soft tissue mass). It's formation of at the site is common.
- Noncontiguous spinal disease (eg, disease at more than one level) is uncommon, although in one South African series it was described in 16 of 98 cases.
- The most common symptom is local pain, which increases in severity over weeks to months, sometimes in association with muscle spasm and rigidity. The muscle spasm can extend beyond the diseased area. In some cases, a characteristic erect posture and "**aldermanic**" gait may be observed in which the patient walks with short, deliberate steps to avoid jarring of the spine. Constitutional symptoms such as fever and weight loss are present in less than 40 percent of cases.
- **The diagnosis of musculoskeletal TB** is established by **microscopy and culture** of infected material. Tissue may be obtained by needle aspiration and/or biopsy; computed tomography (CT) guidance is useful in regions where available.
- CT or MRI reveals the characteristic lesion
- The diagnosis of tuberculous arthritis can be established by synovial biopsy. Synovial fluid may be examined, but findings are usually nonspecific; the white cell count can be high or low, with preponderance of either neutrophils or lymphocytes.

- **Treatment** of musculoskeletal tuberculosis consists of **antimicrobial therapy**. In some cases, **surgical intervention** is also warranted.
- **Surgical intervention** is warranted for patients in the following circumstances:
    - Patients with spinal disease and **advanced neurological deficits**
    - Patients with spinal disease and **worsening neurological deficits progressing while on appropriate therapy**
    - Patients with spinal disease and **kyphosis >40 degrees at the time of presentation**
    - Patients with **chest wall cold abscess**

9. TB PERICARDITIS

- Tuberculous pericarditis occurs in approximately 1 to 2 % of patients with pulmonary tuberculosis (TB).
- Develops frequently in HIV-infected patients
- Case fatality rates are as high as 40%
- Direct extension from adjacent mediastinal or hilar lymph nodes, hematogenous spread.
- **Four pathological stages** of tuberculous pericarditis have been described:
    - **Fibrinous exudation** with polymorphonuclear leukocytosis, abundant mycobacteria, and early granuloma formation with loose organization of macrophages and T cells
    - **Serosanguineous effusion** with lymphocytic exudate and high protein concentration; tubercle bacilli present in low concentrations
    - **Absorption of effusion** with granulomatous caseation and pericardial thickening with subsequent fibrosis
    - **Constrictive scarring**; fibrosing visceral and parietal pericardium contracts on the cardiac chambers and may become calcified, leading to constrictive pericarditis, which impedes diastolic filling.

Clinical features

- The onset may be subacute, although an acute presentation
- Dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible. (Cough -94%, Dyspnea - 88%, Chest pain (often pleuritic) - 76%, Night sweats - 56%, Orthopnea - 53%, Weight loss - 48%)
- An effusion eventually develops in many cases; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear.

Investigation

- Echo, CT, or MRI shows effusion and thickness across the pericardial space.
- Pericardiocentesis under echocardiographic guidance; exudative fluid, with a high count of predominantly lymphocytes and monocytes; hemorrhagic effusion is common.
- Direct smear examination is very rarely positive.
- Culture - +ve *in up to 2/3rd of cases, pericardial* biopsy has a higher yield.

Complications:

- Chronic constrictive pericarditis, tamponade calcification, which may be visible on a chest radiograph.
- The approach to antituberculosis therapy for treatment of tuberculous pericarditis is generally the same as that for pulmonary tuberculosis.

Miliary tuberculosis

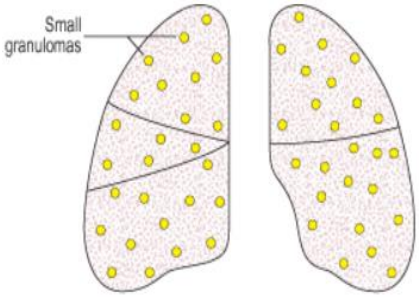
- The term miliary TB was originally a pathologic and then a radiographic description; it is now **used to denote all forms of progressive, widely disseminated hematogenous TB**.
- The term also may be used more broadly (and incorrectly) by some to denote involvement at multiple sites, whether or not disease presents with the classic radiographic or pathologic nodular appearance characteristic of hematogenous spread.
- Miliary TB is **a severe manifestation of tuberculosis.**
- **Risk factors** include;
    - Extremes of ages (very young and elderly)
    - Malnourished
    - Altered cell mediated immunity such as HIV, CKD, and solid organ transplant recipients.
- The most frequently affected organs are liver, spleen, lung, lymph nodes, meninges, bone marrow and the adrenal glands.
- The **clinical presentation ranges from** severe acute forms involving **septic shock, multiple organ dysfunction syndrome** and **ARDS to** a more frequent **subacute presentation with insidious symptoms** such as trivial physical examination.
- Miliary TB can arise as a result of progressive primary infection or via reactivation of a latent focus with subsequent spread via the bloodstream
- ***Physical findings*** include;
    - **Hepatomegaly, splenomegaly, and lymphadenopathy**.
    - Eye examination may reveal **choroidal tubercles**, **which are pathognomonic of military TB,** in up to 30% of cases.
    - **Meningismus** occurs in fewer than 10% of cases

Investigation and diagnosis

- Chest radiography → can show;
    - ✓ Micronodular infiltrates (miliary pattern) in 2/3rd of patients that assist in the diagnosis of military TB.
    - ✓ No radiographic abnormality
    - ✓ Large infiltrates, interstitial infiltrates
- Sputum-smear microscopy is negative in most cases.
- Anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and
- Leukemoid reactions, and polycythemia.
- Elevation of alkaline phosphatase
- Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients.

- If it goes unrecognized, miliary TB is lethal

NB; The term "miliary" was coined in 1700 by John Jacobus Manget, who likened the appearance of the involved lung to millet seeds, with its surface covered with small, firm white nodules. some authors use disseminated TB interchangeably with miliary TB. however, miliary TB in fact refers more specifically to disseminated TB which presents with a millet-seed-like appearance on a chest x ray, when the disease is spead by blood throughout the lungs.



Picture; miliary TB

3.3 RVI-TB Coinfection

☛ Refer under RVI section of Nitsbin (click here → RIV - TB *coinfection*)

3.4 Management of TB

Principles of TB Treatment

1. **Chemotherapy → Anti TB drugs**
2. **Adjuvant therapy**
    - Include **steroid therapy and pyridoxine**
    - Indication for steroid
        - CNS TB (TB meningitis, tuberculoma)
        - Pericarditis
        - Miliary TB with acute air blocking syndrome
        - TB adrenalitis
    - **Supplement with Pyridoxine (Vit B6), 25 to 50 mg, PO daily to prevent peripheral neuropathy from Isoniazid side effect**
3. **Nutritional therapy**
4. **Family screening; should be done for**
    - Those under five children
    - Pregnant ladies
    - Elders, age >65 yrs
    - All HIV /AIDS pts at home
5. **Follow up**

The aims of treatment of Tuberculosis are:

- To cure the patient from TB
- To prevent death from TB disease and its late effects
- To prevent relapse of TB
- To prevent the development of acquired drug resistance, and

- To decrease TB transmission

Pre-treatment Evaluation and preparation for treatment

- *Before you put patients on anti-TB drugs, gather baseline information on: how diagnosis of TB has been made, check for confirmatory Bacteriologic information, determine the site of involvement, offer HIV test, assess risk for drug resistance and co-morbid conditions like pregnancy, renal or liver disease …*

First line drugs;

- **Rifampicin(R)** → The most bactericidal and potent sterilizing agent.
- **Isoniazid (H)** → Highly bactericidal especially in the first few days
- **Pyrazinamide (Z)** → Bacteriostatic and Only active in acidic environment and bacilli inside macrophages
- **Ethambutol (E) -** Bacteriostatic and effective to prevent drug resistance when administered with other potent drugs.

- In order to achieve the designed aim of treatment, anti-TB treatment regimen should not only be designed considering effectiveness and safety of the drugs but also the treatment needs to be administered;
  - In appropriate combination of drugs
  - In the correct dosage
  - Regularly taken by the patient, and
  - For a sufficient period of time.
- Dose→ HRZE - 5,10,25,15 mg/kg for adults…. HRZE -10,15,35,20 mg/kg for pediatrics. Children weighing ≥ 25kg can be treated using recommendation for adults.

Table: First line TB treatment adult and pediatric dosing chart using body weight bands

Adult and pediatric ≥25 kg weight			Pediatrics			
Patient weight band (kg)	Regimen and dose in two phases		Daily dose (mg/kg weight)	Regimen and dose in two phases		
	Intensive: 2(RHZE);	Continuation: 4(RH);		Intensive: 2(RHZ) (E)		Continuation: 4(RH)
	RHZE ;150/75/400/275 mg	RH; 150/75 mg		RHZ; 75/50/150 mg	E; 100 mg	RH; 75/50 mg
20-29	1 ½	1 ½	4-7kg	1	1	1
30-39	2	2	8-11kg	2	2	2
40-54	3	3	12-15kg	3	3	3
≥55	4	4	16-24kg	4	4	4
			25+kg	Adult dosages recommended		
Note: all TB patients on treatment need daily Pyridoxine 50mg tablet supplement.						

Second line drugs; drugs (including injectable fluoroquinolones and aminoglycosides) which are used for the treatment of Drug resistant TB

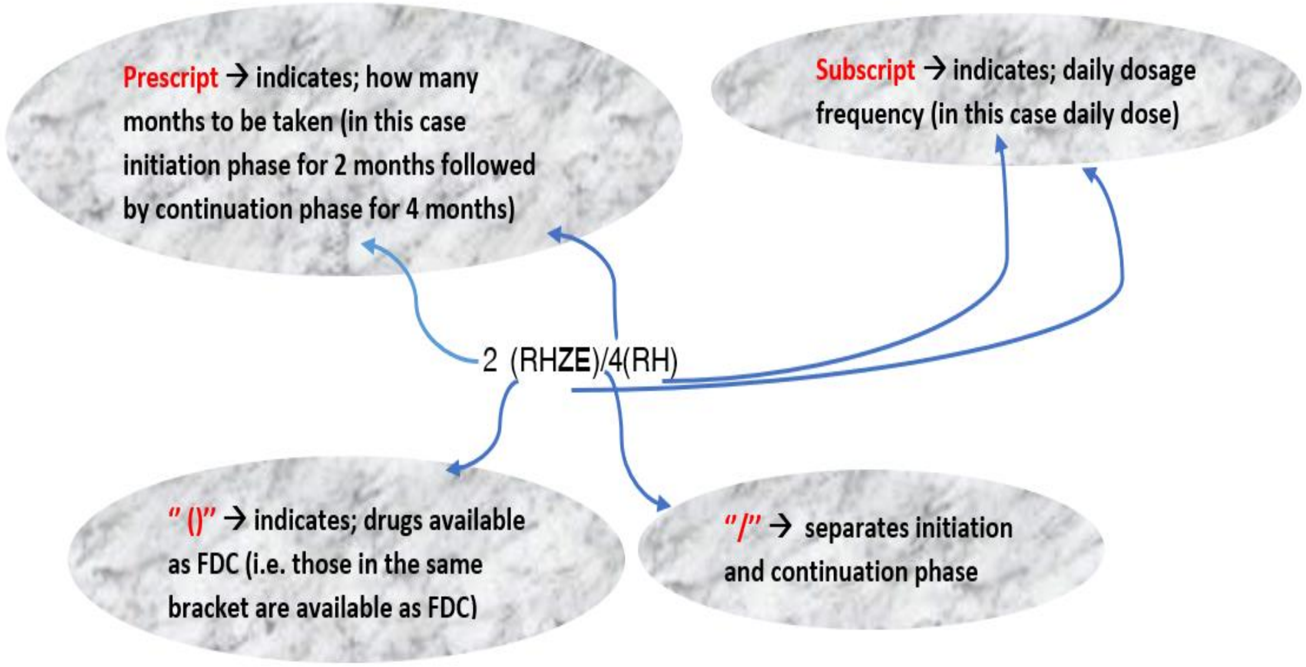
- Amikacin (Am)
- Capreomycin (Cm)
- Cycloserine (Cs)
- Ethionamide (Eto)
- Kanamycin (Km)
- Levofloxacin (Lfx)
- *para*-Aminosalicylic acid (PAS)
- Streptomycin (S) → 1st line in some clinical conditions

TB treatment is administered in two phases:

- **Intensive (initial) phase**: aims to render the patient non-infectious by rapidly reducing the bacillary load in the sputum and brings clinical improvement in most patients receiving effective treatment.
- **Continuation phase:** aims to sterilize the remaining semi-dormant bacilli and is important to ensure cure/ completion of treatment and prevent relapse after completion of treatment.

Dosing frequency and regimens of Anti TB drugs:

- Daily administration of all doses of the 6 months.
- All New TB patients are presumed to have drug-susceptible TB unless they have developed active TB after known contact with a patient documented to have drug-resistant TB.
- The preferred regimens (unless there is special consideration) are ***2RHZE/4RH***
- TB treatment should be implemented under DOT (directly observed treatment) in Ethiopia considering the high TB/HIV and MDR-TB prevalence.
- For patients who have developed active TB after known contact with a patient documented to have drug-resistant TB; treatment should be decided based on rapid DST (Drug Susceptibility Test) result. While awaiting DST result, the patient may be initiated treatment with the regimen based on the DST of the presumed source case as they are likely to have a similar drug resistance pattern.
- In all **previously treated TB patients** who require re-treatment, specimen for rapid molecular-based **DST for first line TB drugs should be obtained** at or before the start of treatment to inform the choice of appropriate treatment regimen.
- While awaiting the DST result, the standard first line treatment regimen **2(RHZE)/4(RH) is recommended for previously treated TB patients**
- ***Note*** that, re-treatment regimen for 08 months with addition of streptomycin should no longer be prescribed for patients coming to receive treatment for repeated TB episode.


Prescript → indicates; how many months to be taken (in this case initiation phase for 2 months followed by continuation phase for 4 months)
Subscript → indicates; daily dosage frequency (in this case daily dose)
2 (RHZE)/4(RH)
" ()" → indicates; drugs available as FDC (i.e. those in the same bracket are available as FDC)
"/" → separates initiation and continuation phase

Diagram; explanation of terminologies in anti TB prescription

Treatment of Extra-pulmonary TB (EPTB)

- Extra-pulmonary tuberculosis (EPTB) is generally treated with the same regimen as pulmonary tuberculosis.
- The guiding principles for patient registration, regimen designing, monitoring of treatment and outcome definitions are similar to patients with pulmonary TB.
- Additional considerations in EPTB Treatment:
  - ✓ *Treat patient with extra-pulmonary TB involving any site **for 6 months** with standardized first-line regimen with the **exception of CNS TB** (meningitis, tuberculoma) and **Osteoarticular TB** (including vertebral bones, joint and osteomyelitis), which require prolongation of the **continuation phase** for **10 months and for a total of 12 months: 2RHZE/10RH***
  - ✓ An initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8weeks should be used for patients with **Tuberculosis meningitis and/or pericarditis** to improve outcome and reduce complications.
  - ✓ Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a tapering course over 6 to 8 weeks. Children (<14 years) should be given prednisolone 4mg/kg/24 hrs (or equivalent dose dexamethasone: 0.6 mg/kg/24 hrs) for 4 weeks, followed by a tapering course over 4 weeks.

Precautions during treatment with 1st line anti-TB medicines

Treatment of patients with renal failure:

- Consult expert.

- If not possible to consult, then **avoid Streptomycin & Ethambutol**; therefore, the recommended regimen is **2RHZ/4RH.**

Treatment of patients with (previously known) liver disorder (e.g. hepatitis, cirrhosis):

- Most anti-TB medicines can cause liver damage.
- **Do not give Pyrazinamide** because this is the most hepatotoxic anti-TB medicine.
- Hence, for TB patients with liver disease, recommended regimens are: **2RHES/6RH** or 9RHE.
- If the patient has **severe liver damage (e.g.** In the case of **jaundice**), the treatment regimen should be changed to **2HES /10 EH.**
- The dose of Rifampicin for these patients should not exceed 8mg/kg and Isoniazid dose should not exceed 4 mg/kg.

Pericardial tuberculosis

- For patients with pericardial tuberculosis, the same regimen (as pulmonary) of anti-TB treatment is recommended (need expert opinion in diagnosis and treatment).
- Corticosteroids are recommended as adjunctive therapy for 11 weeks during the first period of anti-tuberculosis therapy with *tapering as shown in the table below*.

Table; Prednisone dose for adult TB patients with TB pericarditis

Weeks of treatment	**Prednisolone dosage**
1-4	60mg/day
5-8	30mg/day
9-10	15mg/day
11th week	5mg/day (then discontinue at end of 11th week)

Tuberculous meningitis

- Patients presenting with more severe brain impairment such as drowsiness, neurological signs, or coma have a greater risk of neurological sequelae and higher mortality.
- Chemotherapy should be initiated with **2RHZS/7RH or 2RHZS/10RH**
- Adjunctive corticosteroid therapy is recommended for all patients.

  First line
    - **Dexamethasone**, 12 mg/day (8 mg/day for children < 25 kg) for 3 weeks and then decreased gradually during the subsequent 3 weeks.

  Alternative
    - **Prednisolone,** 60mg/day (2-4mg/kg/day for children), for 3 weeks, then tapered off gradually over the following 3 weeks

Treatment during pregnancy and breast-feeding

- **Avoid Streptomycin** because of the risk of toxic effects on the fetus.
- Chemotherapy should not be discontinued during breast-feeding.
- When a breast-feeding mother has Pulmonary TB, the infant should, regardless of prior vaccination with BCG, be given chemo-prophylaxis and then be vaccinated with BCG if not previously vaccinated.

3.5 Baby of a mother with Active tuberculosis

- If the mother has active lung tuberculosis (sputum smear positive TB) and was treated for less than two months before birth or was diagnosed with tuberculosis after birth:
  - Reassure the mother that it is safe for her to breastfeed her baby;
  - **Do not give** the tuberculosis vaccine (**BCG) at birth**
  - **Give prophylactic isoniazid 5 mg/kg**, **PO, daily**

Follow up and management of baby of mother with active TB

- **At the age of 6 weeks**, the baby should be re evaluated
  - **If** there are any findings suggestive of **active disease**, **start full anti TB** treatment according to national guidelines.
  - **If** the baby is doing well and tests are **negative**, **continue prophylactic isoniazid** to complete **6 months**
- **Delay BCG vaccine until two weeks after treatment is completed.**
- **If BCG was already given**, **repeat BCG 2 weeks after the end of the isoniazid treatment.**

Refer updated NICU guideline for more

Follow up and monitoring treatment responses of adult patients

- During treatment follow-up, monitoring of patient's progress involves:
  - **Clinical assessment** (including **signs and symptoms, weight** measurement)
  - **Follow-up AFB** sputum examination, and
  - Detection and treatment of **adverse drug reaction**

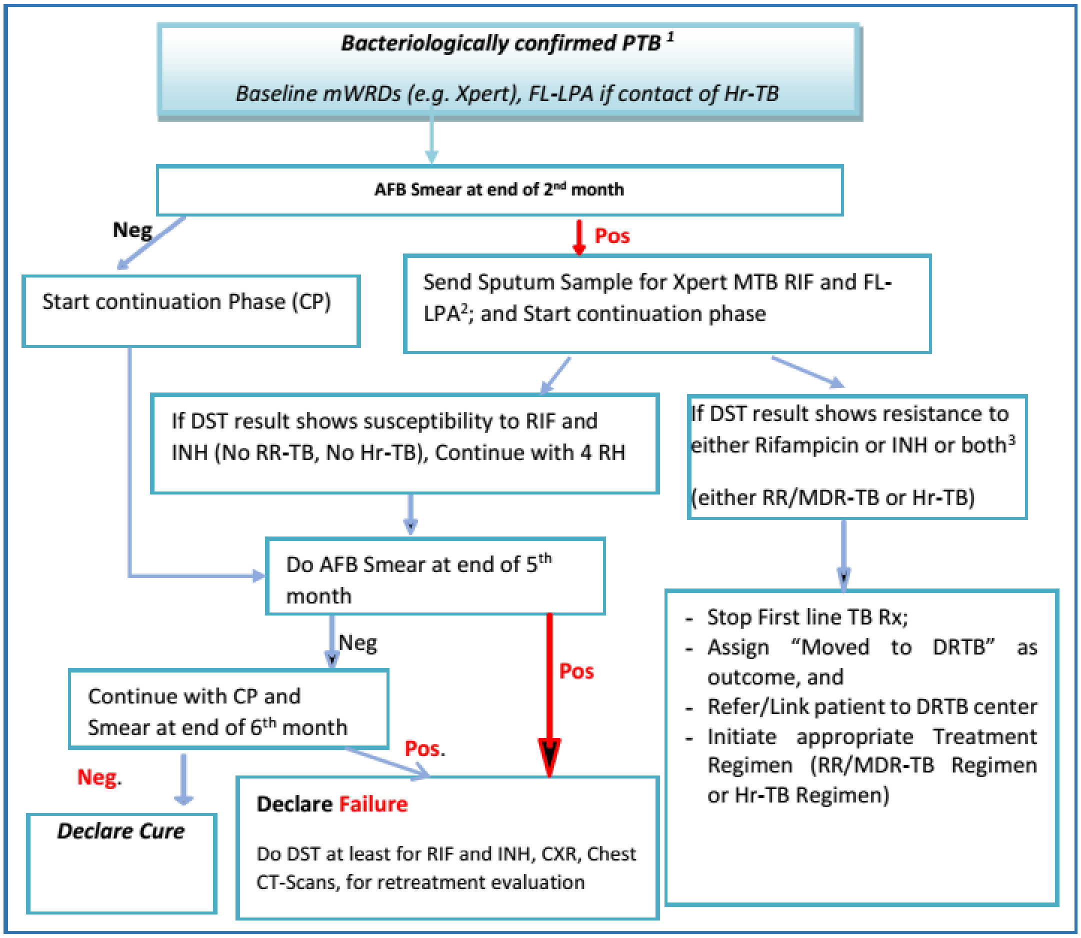
A) Clinical Monitoring of TB patients:

- During scheduled visit, a patient receiving TB treatment should be checked for:
  - ✓ Health worker or a community TB treatment supporter must observe and ensure each patient swallows every single dose of the medicines; this is called directly observed treatment or DOT
  - ✓ Persistence or reappearance of clinical feature of TB, including weight monitoring
    - Weight is a useful indicator of clinical improvement especially in children and should be monitored monthly.

- ✓ Treatment adherence by reviewing the "treatment supporter card" or UNIT TB register Risk for developing acquired drug resistance, and need for DST (Drug Susceptibility Test) screening, Occurrence of Adverse drug reaction, and Development of TB complications.
- ✓ Unsatisfactory response to treatment beyond two months of treatment should alarm the possibility of drug resistance or alternative diagnoses.

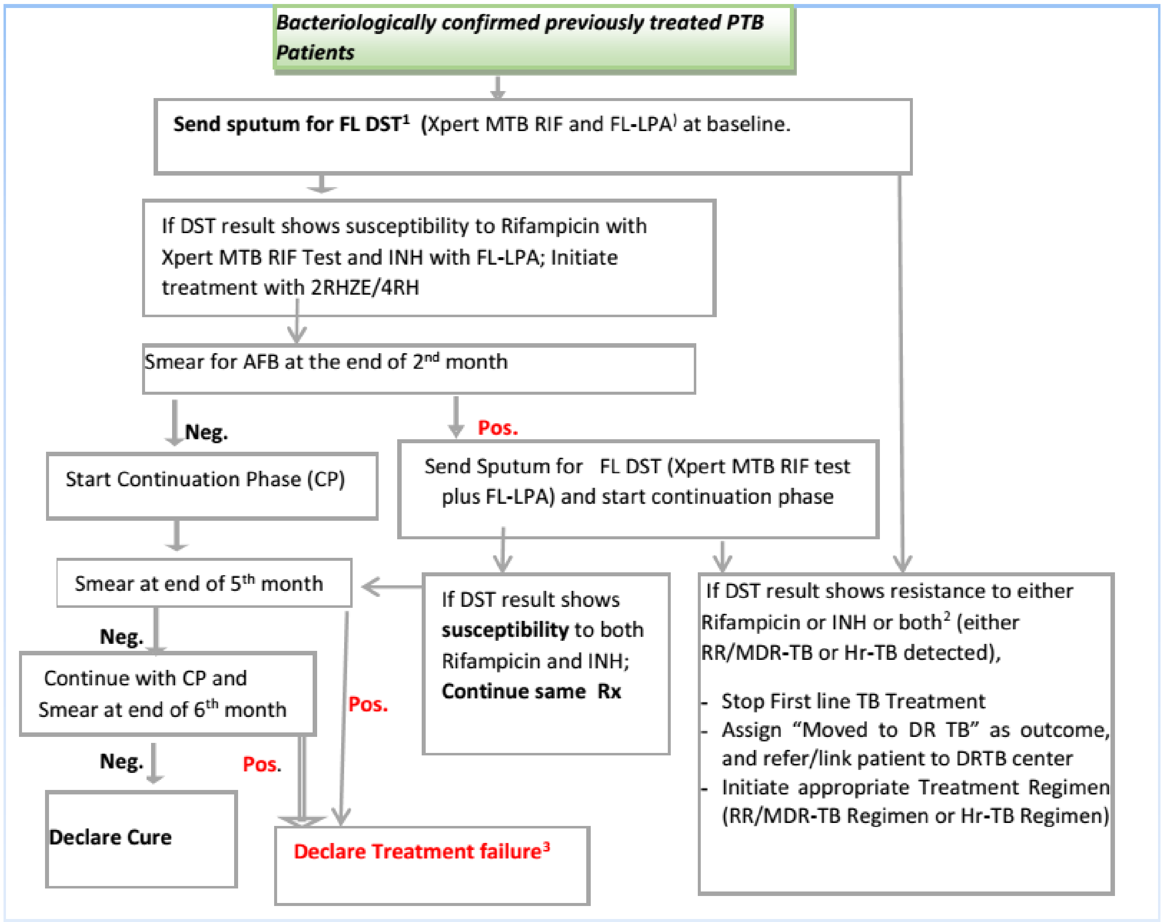
B) Bacteriologic monitoring of bacteriologically confirmed pulmonary TB patients:

- Besides the clinical monitoring, bacteriologically confirmed pulmonary TB patients (i.e. those diagnosed by identification of bacilli by smear microscopy, culture or Xpert MTB/RIF assay) need their sputum to be checked using **AFB microscopy**.
- Molecular technique like Xpert MTB/RIF assay cannot be used to monitor treatment response as the technique **may give false positive result** as it identifies dead bacilli.
- Follow-up sputum examination is done for all **new smears +ve TB** cases at the **2nd, 5th and 6th month.**
    - ☛ If smear result is **+ve at 2nd month**, a **repeat** sputum smear examination is done at the **3rd month** and if it is **still positive**, the sample must be **sent for DST**.
    - ☛ If smear result is **+ve at 5th month or later**, it is declared that **treatment has failed** and patient will be **started on re-treatment regimen** and sputum is examined for DST.
    - ☛ If smear is **-ve at 5th and 6th month** of follow-up, patient is **declared cured.**
- Follow-up sputum examination is done for all **previously treated smear positive TB** cases **at 3rd, 5th and 8th month**.
    - ☛ If smear result is **+ve at the 3rd month**, sample must be **sent for DST**.
    - ☛ If smear result is **+ve at the 5th month or later,** it is declared that **treatment has failed** and patient must be **started on 2nd line** treatment regimen pending the DST result.
    - ☛ If smear is **-ve at 5th and 8th month** of follow-up, patient is **declared cured.**


Bacteriologically confirmed PTB [1]
Baseline mWRDs (e.g. Xpert), FL-LPA if contact of Hr-TB
AFB Smear at end of 2nd month
Neg
Pos
Start continuation Phase (CP)
Send Sputum Sample for Xpert MTB RIF and FL-LPA[2]; and Start continuation phase
If DST result shows susceptibility to RIF and INH (No RR-TB, No Hr-TB), Continue with 4 RH
If DST result shows resistance to either Rifampicin or INH or both[3]
(either RR/MDR-TB or Hr-TB)
Do AFB Smear at end of 5th month
Neg
Pos
- Stop First line TB Rx;
- Assign "Moved to DRTB" as outcome, and
- Refer/Link patient to DRTB center
- Initiate appropriate Treatment Regimen (RR/MDR-TB Regimen or Hr-TB Regimen)
Continue with CP and Smear at end of 6th month
Pos.
Neg.
Declare Cure
Declare Failure
Do DST at least for RIF and INH, CXR, Chest CT-Scans, for retreatment evaluation

[1]Bacteriolgically confirmed TB patients include those diagnosed by positive result on either mWRDs (e.g. Xpert MTB/RIF Assay), AFB microscopy, or culture. [2]DST may be performed from one sputum sample using Xpert MTB/RIF, LPA or conventional DST based on availability. Information on Rifampicin may be enough to decide on Next Action. [3]if DST result shows resistance to INH but susceptible to Rifampicin; treat with Hr-TB Regimen.

Figure: Sputum AFB Follow-up for Bacteriologically Confirmed PTB Patients


Bacteriologically confirmed previously treated PTB Patients
Send sputum for FL DST¹ (Xpert MTB RIF and FL-LPA) at baseline.
If DST result shows susceptibility to Rifampicin with Xpert MTB RIF Test and INH with FL-LPA; Initiate treatment with 2RHZE/4RH
Smear for AFB at the end of 2nd month
Neg.
Pos.
Start Continuation Phase (CP)
Send Sputum for FL DST (Xpert MTB RIF test plus FL-LPA) and start continuation phase
Smear at end of 5th month
If DST result shows susceptibility to both Rifampicin and INH; Continue same Rx
If DST result shows resistance to either Rifampicin or INH or both² (either RR/MDR-TB or Hr-TB detected),
- Stop First line TB Treatment
- Assign "Moved to DR TB" as outcome, and refer/link patient to DRTB center
- Initiate appropriate Treatment Regimen (RR/MDR-TB Regimen or Hr-TB Regimen)
Neg.
Continue with CP and Smear at end of 6th month
Pos.
Neg.
Pos.
Declare Cure
Declare Treatment failure³

[1] DST may be performed from one sputum sample using Xpert MTB/RIF, LPA or conventional DST based on availability. Information on rifampicin and INH DST may be enough to decide on Next Action.

[2] If DST result shows resistance to INH but susceptible to Rifampicin; treat with Hr-TB Regimen.

[3] A patient who has failed second course of full TB treatment requires further evaluation and consultations. Such patients require chest imaging, Full DST for FLDs, and further workup to establish the cause for treatment failure. Referral to DR-TB TICs and/or consultations are required in such cases.

Fig. **Flow Chart for Sputum AFB Follow-up for bacteriologically confirmed *previously treated* PTB Patients**

Table; Common side effects of Anti-TB drugs

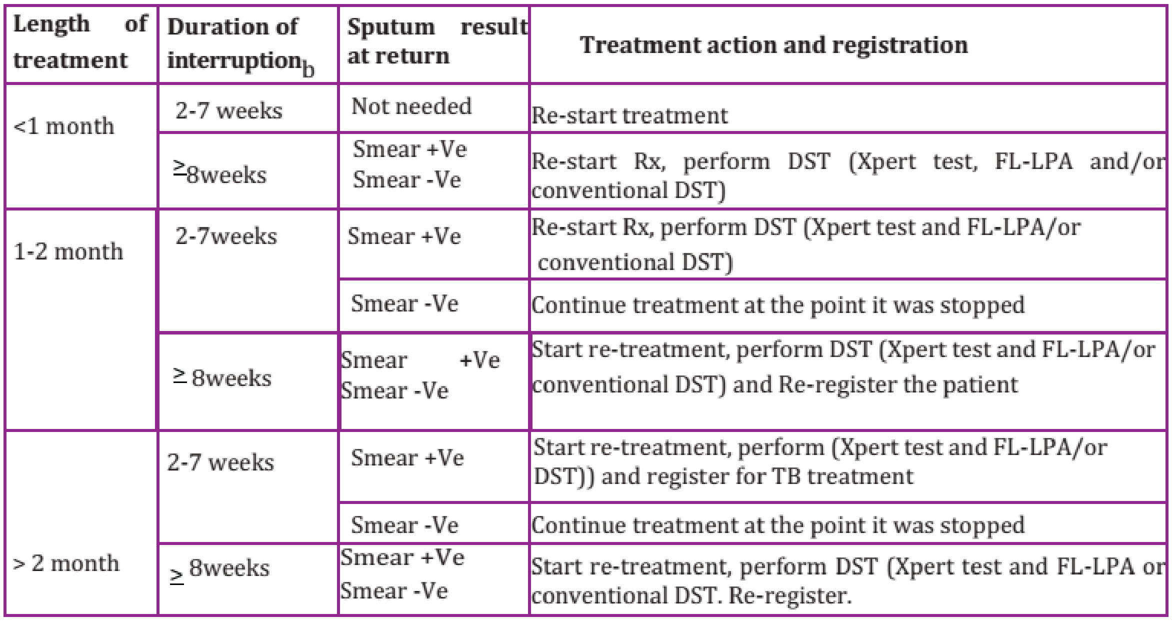
Drug	Side effects ➢ all are hepatotoxic but Pyrazinamide is most common hepatotoxic anti TB drug
R/RMP/ (Rifampicin)	➢ **Body fluid discoloration** ➢ **Drug-Drug interaction with Nevirapine in RVI pt's** ➢ Hepatitis, Thrombocytopenia, fever
H /INH/ (Isoniazid)	➢ **Peripheral neuropathy** → can be **prevented by** prescribing INH together with **Pyridoxine (Vit.B6)** ➢ Hepatitis, hypersensitivity Reaction
Z (pyrazinamide)	➢ **Hepatitis,** Hyperuricemia, Teratogenic
E (Ethambutol)	Mnemonic → E for eye ➢ **Reversible optic neuritis**

	➢ Color blindness (especially for red and green colors) ➢ Scotoma Hypersensitivity reaction, rash
S (Streptomycin)	➢ Nephrotoxicity (all aminoglycosides are Nephrotoxic) ➢ Congenital deafness (CN VIII damage)

N.B

- Drug susceptibility testing (DST) on all TB isolates.
- HIV testing on all cases.
- Begin initial therapy before DST results are back.
- Never add a single drug to a failing regime
- Adherence to therapy is major issue--DOT for all.

Table: Management of New Pulmonary TB Treatment Interrupters[a]

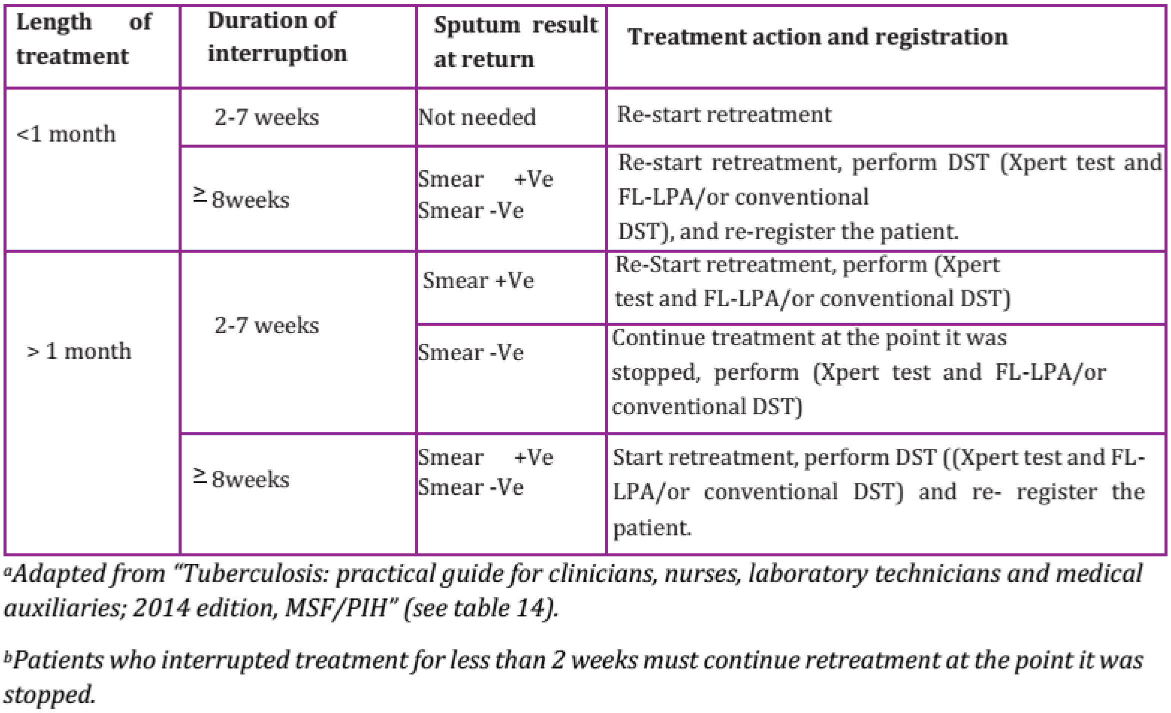


Length of treatment	Duration of interruption[b]	Sputum result at return	Treatment action and registration
<1 month	2-7 weeks	Not needed	Re-start treatment
	≥8weeks	Smear +Ve Smear -Ve	Re-start Rx, perform DST (Xpert test, FL-LPA and/or conventional DST)
1-2 month	2-7weeks	Smear +Ve	Re-start Rx, perform DST (Xpert test and FL-LPA/or conventional DST)
		Smear -Ve	Continue treatment at the point it was stopped
	≥ 8weeks	Smear +Ve Smear -Ve	Start re-treatment, perform DST (Xpert test and FL-LPA/or conventional DST) and Re-register the patient
> 2 month	2-7 weeks	Smear +Ve	Start re-treatment, perform (Xpert test and FL-LPA/or DST)) and register for TB treatment
		Smear -Ve	Continue treatment at the point it was stopped
	≥ 8weeks	Smear +Ve Smear -Ve	Start re-treatment, perform DST (Xpert test and FL-LPA or conventional DST. Re-register.

[a] Adapted from "Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries; 2014 edition, MSF/PIH"

[b] Patients who interrupted treatment for less than 2 weeks must continue treatment at the point it was stopped.

Table: Management of Retreatment Patients Who Interrupted Treatment for 2 Weeks or more[a]



Length of treatment	Duration of interruption	Sputum result at return	Treatment action and registration
<1 month	2-7 weeks	Not needed	Re-start retreatment
	≥ 8weeks	Smear +Ve Smear -Ve	Re-start retreatment, perform DST (Xpert test and FL-LPA/or conventional DST), and re-register the patient.
> 1 month	2-7 weeks	Smear +Ve	Re-Start retreatment, perform (Xpert test and FL-LPA/or conventional DST)
		Smear -Ve	Continue treatment at the point it was stopped, perform (Xpert test and FL-LPA/or conventional DST)
	≥ 8weeks	Smear +Ve Smear -Ve	Start retreatment, perform DST ((Xpert test and FL-LPA/or conventional DST) and re- register the patient.

[a] *Adapted from "Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries; 2014 edition, MSF/PIH" (see table 14).*

[b] *Patients who interrupted treatment for less than 2 weeks must continue retreatment at the point it was stopped.*

3.6 Drug resistant TB

- TB is considered drug-resistant (DR) when the TB causative agent (mycobacterium tuberculosis) is not killed by one or more of the available anti-TB medicines.
- Medicine resistant TB can be primary or secondary (acquired).
    - **Primary resistance** → it is medicine **resistance among new cases**; it is resistance to one or more anti-TB medicines **in a person who has never been previously treated** for TB.
    - **Secondary resistance** → it is medicine **resistance among previously treated cases**; in people diagnosed with TB who start anti-TB treatment and subsequently acquire resistance to one or more of the medicines used during the treatment.
- Both medicines susceptible and resistant MTB spread in the same manner.
- There are five different types of drug resistance: Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be M. tuberculosis:
    - **Rifampicin resistant TB**: resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.
    - **Multidrug-resistance (MDR):** Resistance to at least Isoniazid and Rifampicin.
    - **Multidrug- or rifampicin-resistant TB (MDR/RR-TB):** is the term used to group MDR-TB and RRTB cases together as MDR/RR-TB; both MDR-TB and RR-TB cases are eligible for treatment with MDRTB regimens. MDR/RR-TB usually refers to all patients affected by either MDR-TB or RR-TB.

- **Isoniazid-resistant TB (Hr-TB):** TB caused by Mycobacterium tuberculosis strains resistant to isoniazid and susceptible to rifampicin
- **Pre-XDR-TB:** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RRTB and that are also resistant to any fluoroquinolone.
- **Extensively drug-resistant TB (XDR-TB):** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug (Bedaquiline or Linezolid).

Since XDR-TB progresses from MDR-TB in two steps, the term "pre—XDR-TB" was introduced to recognize MDR-TB with additional resistance to either one but not both of these classes of medicines.

- **The clinical features of drug susceptible and drug resistant TB are the same**
- **Investigations**
    - Direct smear microscopy
    - Line Probe Assay (LPA) directly from the sputum specimen or cultured sample
    - Culture and DST
    - Gene Xpert MTB/RIF test
    - CXR
    - HIV test
    - **Other tests:** CBC, U/A, FBS, LFT, RFT, Serum electrolyte, TSH, HCG, Audiometric test
- Definitive diagnosis of Drug-resistant TB depends on laboratory diagnosis through Medicine Susceptibility testing (DST); it requires that *M.tuberculosis* is isolated and drug susceptibility test is completed.

MDR - TB treatment in Ethiopia

- Duration of treatment
    - ✓ Intensive phase → the injectable agents is used for a minimum of 8 months and at least 4 months after culture conversion
    - ✓ Continuation phase →The total treatment is for a minimum of 18 months beyond culture conversion
- Patients with laboratory confirmed Rifampicin-/Multi drug resistant TB (RR/MDR-TB) require treatment with second-line TB regimens. MDR-TB Patients with strains resistant to at least rifampicin and Isoniazid are treated with standardized second line treatment regimen for at least 18—21 months.

- If you suspect Drug resistant TB refer to a specialized hospital having TB Treatment center
- Detailed management of Drug resistance TB is beyond the scope of this text book. Readers are advised to read;
    - Guidelines for Clinical and Programmatic Management of TB, TB/HIV, DR-TB and Leprosy in Ethiopia, 7th edition, 2021
    - *National Programmatic management of Drug resistant TB in Ethiopia, FMOH, December 2019* and
    - *Standard treatment guideline for general hospitals in Ethiopia, 4th edition, 2021*

Chapter 4; Lung cancer (የሳንባ ካንሰር)

Dr. Asmare.W

Epidemiology

- Incidence peaks 55 - 65 years
- **leading cause of cancer-related death** in North America and Europe, killing over three times as many men as prostate cancer and nearly twice as many women as breast cancer.
- Most preventable b/c 90 % associated with smoking
- Adenocarcinoma. highest (32%), squamous (28%) after 25 years age

Etiology and Risk factors

- A number of environmental and lifestyle factors have been associated with the subsequent development of lung cancer, of which **cigarette smoking is the most important.**
- Smoking
    - The primary risk factor for the development of lung cancer is cigarette smoking, which is estimated to account for approximately 90 % of all lung cancers.
    - The risk of developing lung cancer for a current smoker of one pack per day for 40 years is approximately 20 times that of someone who has never smoked.
    - Factors that increase the risk of developing lung cancer in smokers include the extent of smoking and exposure to other carcinogenic factors, such as asbestos.
    - Carcinogens and tumor promoters in
        - ✓ Pack year=dose X length, (RR-13X,1.5X)
        - ✓ Sex - women more susceptible
        - ✓ Quitting/prevent starting
    - Decreases with cessation of smoking but may never return to the nonsmoker level.
- Genetic factors
    - Genetic factors can affect both the risk for and prognosis from lung cancer.
    - Although the genetic basis of lung cancer is still being elucidated, there is a clearly established familial risk **(most patients have +ve family hx of lung ca).**
- Radiation therapy (RT)

- can increase the risk of a second primary lung cancer in patients who have been treated for other malignancies.

- **Environmental toxins**
  - These include exposure to second-hand smoke, asbestos, radon, metals (arsenic, chromium, and nickel), ionizing radiation, and polycyclic aromatic hydrocarbons.
- **Pulmonary fibrosis**
  - The risk for lung cancer is increased approximately sevenfold in patients with pulmonary fibrosis. This increased risk appears to be independent of smoking.
- **HIV infection**
  - The incidence of lung cancer among individuals infected with HIV is increased compared with that seen in uninfected controls.
- **Alcohol**
- **Dietary factors**
  - various dietary factors (antioxidants, cruciferous vegetables, and phytoestrogens) may reduce the risk of lung cancer, but the role of these factors is not well established.
  - As an example, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study actually showed an increase in lung cancer among smokers with dietary supplementation of beta-carotene.

Pathology

- Lung ca arising from respiratory epithelium: bronchi, bronchiole, alveoli
- Predominant types include:

1) **Non-small cell lung cancer** (NSCLC)
   - NSCLC is the most common form of lung cancer and is divided into the following types:
     - Squamous cell carcinoma (SCC)
     - Adenocarcinoma
     - Large cell carcinoma
     - Carcinoid tumors
2) **Small cell lung cancer (SCLC)**
   - **Primary pulmonary lymphoma**
   - 88% primary lung ca are 4 cell types
     - Squamous(epidermoid)ca
     - Small cell ca (oat cell)
     - Adenocarcinoma (Broncho alveolar)
     - Large cell (anaplastic)ca
   - 11% undifferentiated
     - Carcinoids
     - Gland tumors

- Mesothelioma, lymphoma, sarcomas are not lung ca

Table; Comparison b/n SCLC & NSCLC		
	Small cell lung ca	NSCLC

Type	Oat cell	Squamous, adeno, large cell, bronchoalveolar, mixed
Histology	Scanty cytoplasm, Small hyperchromatic nuclei, indistinct nucleoli, diffuse sheet of cells	Abundant cytoplasm Pleomorphic nuclei Coarse chromatin Prominent nucleoli Glandular/squamous
Molecular	Neuroendocrine property	Absent
Oncogenes/tumor suppressors	RB mutation	Different
Metastasis at presentation	Early	Localized
Treatment response	Chemo + radio	Surgery + radio

1. Squamous Cell carcinoma (SCC)

- Characterized by keratinization and/or intercellular bridges on histopathology.
- SCC was the most frequent histologic type of lung tumor in nearly all studies done prior to the mid-1980s.
- Now, adenocarcinoma is more common than squamous cell carcinoma, particularly in women
- 95% are smokers and males
- Lower rate with metastatic disease
- Associated with HPO (clubbing) and hypercalcemia
- Two thirds of cases **occur centrally**, with involvement of the main stem, lobar, or segmental bronchi.
- It is more commonly associated with HPO (**clubbing**)**,** ***cavitation***, Pancoast syndrome, and hypercalcemia.

2. Adenocarcinoma

- Adenocarcinoma is **the most common type of lung cancer** in contemporary series, accounting for approximately one-half of lung cancer cases.
- The increased incidence of adenocarcinoma is thought to be due to the introduction of low-tar filter cigarettes in the 1960s, although such causality is unproven.
- It is the most common subtype **in women and nonsmokers.**
- Most tumors **occur in the periphery.**
- Subtypes: Bronchi alveolar carcinoma (BAC), now known as adenocarcinoma in situ: Characterized by slow lepidic growth.

3. Large Cell Carcinoma

- Undifferentiated malignant epithelial tumors that lack features of small cell carcinoma and glandular or squamous differentiation.

- They are characterized by large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

4. Carcinoid Tumor

- Pulmonary carcinoid tumors represent about **1 - 5%** of all lung malignancies.
- They are mainly of two types, typical and atypical:
  - Typical carcinoid: < 2 mitoses per 10 high-power fields and absence of necrosis.
  - Atypical carcinoid: > 2 mitoses per 10 high-power fields or presence of necrosis.
- ***Usually occur in those who have never smoked***.
- About ***70%*** of carcinoids develop in the ***proximal airways*** and may be associated with chronic cough, hemoptysis, and bronchial obstruction.
- ***Peripheral carcinoids*** are generally asymptomatic.
- Fewer than **2%** of cases are associated with ***carcinoid syndrome(a combination of symptoms and lesions mostly produced by the release of serotonin from carcinoid tumors of the gastrointestinal tract that have metastasized to the liver; consists of irregular mottled blushing, flat angiomas of the skin, acquired tricuspid and pulmonary stenosis often with regurgitation, occasionally with some minor involvement of valves on the left side of the heart, diarrhea, bronchial spasm, mental aberration, and excretion of large quantities of 5-hydroxyindoleacetic acid.)***
- **Treatment** of carcinoid tumors is different from that of other types of NSCLC:
  - Typical carcinoid: Limited resection with segmentectomy and regional lymph node dissection
  - Atypical carcinoid: Lobectomy and mediastinal lymph node dissection.
  - Metastasis: No known benefit to ***chemotherapy or radiation therapy***. Local treatment of metastases may lead to prolonged remission.

SMALL CELL LUNG CANCER (SCLC)

- SCLC is characterized by proliferation of small cells with scant cytoplasm, ill-defined borders, salt and pepper chromatin, frequent nuclear molding, and a high mitotic count.
- Up to *98%* of patients with SCLC have a history of smoking.
- The natural history of SCLC is early metastasis and death. Vast majority present with metastatic disease (early)
- Unlike NSCLC, SCLC is always considered a systemic disease at diagnosis.
- *Liver, bone, bone marrow, and the central nervous* system are the most commonly affected extrapulmonary organs.
- Usually centrally located.
- Paraneoplastic syndromes related common
- SCLC shows an excellent response to chemotherapy, but almost always recurs.
- Median survival for disease confined to the chest is *4 - 6 months* without treatment.
- For metastatic disease, median survival is *5 - 9 weeks* without treatment.

Summary on pathology

- Adenocarcinoma + nonsmoker → consider another primary site
- Central mass and endobronchial smx → squamous/small cell ca
- Peripheral nodule/mass with pleural → adenocarcinoma/large cell ca
- Squamous and large cell → cavitate 10-20%
- Bronchoalveolar ca → from peripheral airways-radiologically single mass, diffuse, multinodular, fluffy infiltrates

Clinical manifestations

- **Local sign and symptoms**
  - ✓ Asymptomatic 5-15% routine CXR
  - ✓ Cough, hemoptysis, wheezing, stridor, dyspnea, post obstructive pneumonitis (fever) → central / endobronchial primary tumor
  - ✓ Pain-pleursy, chest wall +/-cough, dyspnea → peripheral growth primary tumo
  - ✓ features of lung abscess → (cavitation's/obstruction)

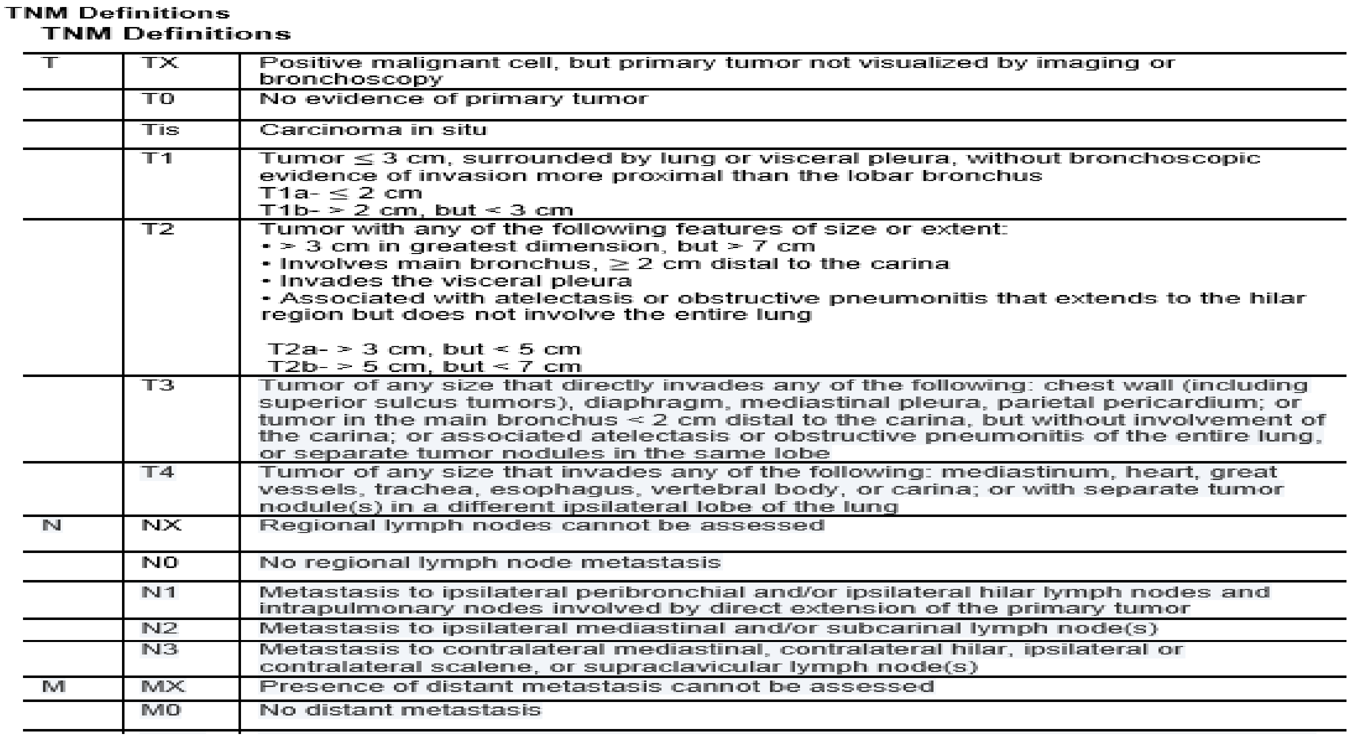
- **Invasion or obstruction of adjacent structures**
  - ✓ Tracheal obstruction
  - ✓ Esophageal compression/dysphagia
  - ✓ Hoarseness → recurrent laryngeal nerve paralysis
  - ✓ Increased hemidiaphragm/dyspnea → phrenic nerve paralysis
  - ✓ Horner's syndrome (sympathetic n. paralysis, enophthalmos, ptosis, miosis, anhidrosis)
- **Growth in regional lymph nodes**
- **Distant metastasis (Hematogeneous)**
  - ✓ At autopsy >95% of SCLC, 80% adenocarcinoma and large cell,50% squamous metastasis.
  - ✓ To any organ;
    - Brain → neurologic deficit (ICSOL)
    - Bone → pain/pathologic fracture
    - Bone marrow → cytopenia
    - Liver → liver dysfunction, obstructive, pain
    - Lymph node → supraclavicular/axilla/groin
    - Spinal cord → compression syndrome, epidural, bone fracture
    - Adrenal gland → Adrenal insufficiency rare but high rate of metastasis (40%).
- **Paraneoplastic syndromes. 5-10%**
    - Common/may be presenting smx
    - May mimic metastasis-inappropriate palliation therapy
    - Relieved by successful treatment of tumor
    - Systemic disease-anorexia, wt loss, cachexia, fever
    - Endocrine syndrome: hypercalcemia, hyponatremia (SIADH), hypokalemia (increased ACTH), Cushing's syndrome

- Skeletal / connective tissue SXX: clubbing/ HPOA (hypertrophic pulmonary osteoarthropathy)
- Neurologic /myopathic syndromes → Myasthenia, peripheral neuropathy, cortical/cerebellar degeneration

Staging

- Determine patient's prognosis and type of treatment.
- Staging differ for SCLC and NSCLC.

1. Staging of NSCLC (TNM staging)



TNM Definitions

TNM Definitions

T	TX	Positive malignant cell, but primary tumor not visualized by imaging or bronchoscopy
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor ≤ 3 cm, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus T1a- ≤ 2 cm T1b- > 2 cm, but < 3 cm
	T2	Tumor with any of the following features of size or extent: • > 3 cm in greatest dimension, but > 7 cm • Involves main bronchus, ≥ 2 cm distal to the carina • Invades the visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung T2a- > 3 cm, but < 5 cm T2b- > 5 cm, but < 7 cm
	T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung, or separate tumor nodules in the same lobe
	T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; or with separate tumor nodule(s) in a different ipsilateral lobe of the lung
N	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor
	N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
	N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M	MX	Presence of distant metastasis cannot be assessed
	M0	No distant metastasis

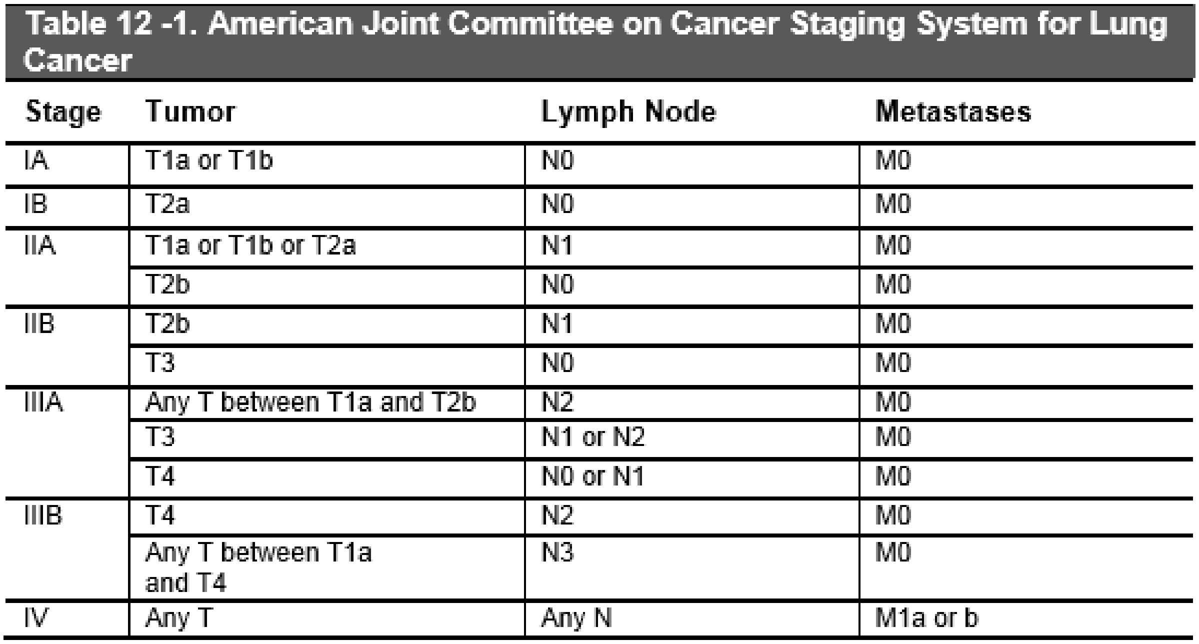


Table 12 -1. American Joint Committee on Cancer Staging System for Lung Cancer

Stage	Tumor	Lymph Node	Metastases
IA	T1a or T1b	N0	M0
IB	T2a	N0	M0
IIA	T1a or T1b or T2a	N1	M0
	T2b	N0	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	Any T between T1a and T2b	N2	M0
	T3	N1 or N2	M0
	T4	N0 or N1	M0
IIIB	T4	N2	M0
	Any T between T1a and T4	N3	M0
IV	Any T	Any N	M1a or b

2. Staging for SCLC

- Simple two-stage system
- L*imited-stage disease* (30%SCLC)
    - disease confined to one hemithorax and regional lymph node (including mediastinal, contralateral hilar, and usually ipsilateral supraclavicular nodes)
- *Extensive-stage disease* (70%)
    - disease exceeding those boundaries cardiac tamponade, malignant pleural effusion, and bilateral pulmonary parenchymal

Diagnosis

- **Goals** – The major goals of the initial evaluation of a patient with suspected lung cancer are to assess the following:
    - Clinical extent and stage of disease
    - Optimal target site and modality for the first tissue biopsy
    - Specific histological subtype
    - Presence of comorbidities, secondary complications, and paraneoplastic syndromes that influence treatment options and outcome
    - Patient values and preferences that influence diagnostic and therapeutic choice
- The preferred approach uses imaging as a road map and invasive biopsy as a tool to confirm both the histopathological diagnosis and the stage of disease.
- When feasible, diagnosis and staging should be established concurrently by targeting for invasive biopsy the abnormality that would yield the most advanced stage. However, some patients will require multiple imaging studies and/or invasive procedures for tissue sampling.
- No single diagnostic algorithm sufficiently addresses the complexity and variation in disease patterns of lung cancer.

- **Clinical suspicion;**
    - The majority of patients who present with clinical signs or symptoms due to lung cancer have advanced disease.
    - The most common presenting manifestations are the following:
        - Cough (50 to 75%)
        - Hemoptysis (25 to 50%)
        - Dyspnea (25 %)
        - Chest pain (20 %)
    - Lung cancer should always be suspected in a current or former smoker with new onset of cough or hemoptysis.
    - Both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) can present with similar symptoms, and few clinical features reliably distinguish them from each other.

  - **Features that suggest SCLC include rapidly progressive symptoms and the presence of paraneoplastic syndromes (eg, syndrome of inappropriate antidiuretic hormone), bulky multi-station mediastinal metastasis, superior vena cava syndrome, and bone and brain metastases.**
  - In contrast, Pancoast's syndrome and hypercalcemia are more frequently encountered in patients with NSCLC.

- CXR → demonstrating the following
  - new or enlarging focal lesion
  - pleural effusion
  - pleural nodularity
  - enlarged hilar or paratracheal nodes
  - endobronchial lesion
  - post-obstructive pneumonia or segmental or lobar atelectasis.
- CT scan of the chest
  - Every patient with suspected lung cancer should undergo CT scan of the chest.
  - IV contrast enhancement is preferable as it may distinguish mediastinal invasion of the primary tumor or metastatic lymph nodes from vascular structures.
  - Images of the liver and adrenal glands should also be included.
  - In most patients, **CT scan assesses;**
    - **the anatomic location and size of the tumor (T)**
    - **nodal (N), and**
    - **metastatic disease of the pleura, liver, and adrenal glands (M).**
  - **CT findings suggestive of malignancy** in a patient with a solitary pulmonary nodule include
    - **large lesion size (eg, >15 mm)**
    - **irregular or spiculated borders**
    - **upper lobe location**
    - **thick-walled cavitation**
    - **presence or development of a solid component within a ground glass lesion, and**
    - **detection of growth by follow-up imaging.**
  - **The finding of multiple nodules in a patient with a known or suspected extra thoracic malignancy strongly suggests pulmonary metastasis.**

- **Whole body PET** (positron emission tomography) scan.
- **Imaging metastatic disease → Indications include;**
  - Patients with focal symptoms, signs, or laboratory tests suggestive of metastatic disease. The modality used depends on the site of suspected metastases
  - Patients with clinical stage III or IV disease have an increased risk of occult intracranial metastasis and may benefit from routine imaging of the brain with magnetic resonance imaging (MRI) or CT if MRI is not available. The rationale for routine brain imaging is the high risk of distant disease in this population, especially metastases to the brain. In

  this setting, an MRI of the brain may be performed for the early detection of brain metastases so that early treatment can be administered before development of neurologic deficits or seizures
  - In patients with clinical stage I/II disease who are candidates for curative resection, there is consensus that routine **brain** imaging with MRI is **not** indicated.
- **lab investigations;** perform the following laboratory studies when chest imaging is suspicious for lung cancer:
  - CBC
  - Electrolytes
  - Liver enzymes
  - LFT
  - RFT
- **pathology;**
  - A diagnosis of lung cancer should not be made without definitive pathology.
  - At a minimum, this involves selecting a biopsy site and obtaining an adequate sample for microscopic examination.
  - *Cytologic specimens can be obtained from the following sites;*
    - Lung → Sputum, transthoracic needle aspirates, and bronchoscopic washings, brushings, or needle aspirates
    - Lymph node → Transthoracic, transbronchial, and transesophageal aspirates
    - Distant metastasis → Pleural fluid, needle aspirates of metastatic tissue.
  - *Core or biopsy tissue can be obtained from the following:*
    - Lung → Endobronchial biopsy (forceps), transbronchial biopsy (forceps or needle), transthoracic (needle) biopsy, surgical biopsy
    - Lymph node → Bronchoscopic and transthoracic needle core biopsy, surgical biopsy.
    - Distant metastasis — Core needle aspirates of metastatic tissue (eg liver, bone, adrenal).

Management of Lung ca

1. NSCLC

- *Stage I and II:*
  - *Surgery is first-line treatment.*
  - *Adjuvant chemotherapy may be useful in selected cases of stage IB disease, especially if the tumor is > 4 cm.*
- *Stage II disease*
  - *surgery followed by adjuvant chemotherapy.*
- *Stage IIIA:*
  - *Most cases are unresectable.*

- *Chemotherapy and/or radiation therapy may be used.*
- *Stage IIIB:*
  - *Combined chemotherapy and radiation therapy is used.*
- *Stage IV:*
  - *Chemotherapy. Radiation therapy for palliation only.*
- ***Special considerations***
  - **Superior sulcus tumor with Pancoast syndrome:**
    - **It** is a constellation of symptoms and signs that include shoulder and arm pain along the distribution of the C8, T1, and T2; Horner's syndrome; and weakness and atrophy of the hand.
    - It is seen in one third of patients with superior sulcus tumors.
  - **Superior vena cava syndrome:**
    - is usually the result of direct obstruction of the superior vena cava by malignancies.
    - Bronchogenic carcinoma is the most common cause.

2. SCLC;

- **Chemotherapy;**
  - **LIMITED DISEASE**
    - response rate of 70 - 80% to chemotherapy and thoracic radiation therapy, with a complete clinical response rate of 50—60%.
  - **EXTENSIVE DISEASE**
    - response rate of 60—80% to chemotherapy, with only 20% of patients achieving complete clinical remission.

PROGNOSTIC FACTORS

- Strongest predictors of survival:
  - Good performance status (Karnofsky scale)
  - Lesser extent of disease
  - Younger age
  - Absence of weight loss
- Other predictors of better survival:
  - Smoking cessation
  - Standard uptake value of the primary tumor on positron emission tomography (PET) scan.
- Histologic subtype not considered a predictor of survival.

BENIGN LUNG NEOPLASM

- Most present as asymptomatic solitary pulmonary nodules, incidentally discovered radiographically.
- About 50% of benign lung neoplasms are **hamartomas.**
- **Broadly divided into epithelial and nonepithelial tumors.**
- **EPITHELIAL NEOPLASMS**

  - Types include: Papilloma; Micro nodular pneumocyte hyperplasia,
  - Papilloma's
    - SQUAMOUS PAPILLOMA, most often associated with cigarette smoking and human papilloma virus. Most occur in central large airways.
- NONEPITHELIAL NEOPLASMS
  - Types include: Solitary fibrous tumors, **Hamartomas**
  - **Hamartomas**
    - Most common benign lung neoplasm in adults
    - More common in men
    - Generally discovered incidentally in the sixth or seventh decade
    - Parenchymal or endobronchial (10%) nodules with characteristic popcorn calcification.
    - Can present as solitary pulmonary nodules.

Management of benign lung tumors

- Most benign lung tumors don't require management.
- It **requires only yearly follow up with imaging.**

Chapter 5; RVI (ኤችአይቪ ኤዲስ)

Dr. Mulualem. G

Clinical features and how to write hx of RVI patient

History

- **Pt's may present with common OI syndromes like TB, Anaemia, cryptococcal meningitis, esophagial candidiasis etc.**
- **If a known RVI patient** → ask the following on your hx
  - For how long he/she was Diagnosed to have RVI in his/her blood
    - e.g a known RVI pt for the past 10 years or you can say 10 years back he/she was told to have RVI (you have to ask what was the presentation at that time and how Dx was made… you may not need to write on your HPI)
  - What is the regimen he/she is taking and for how long s/he was on HAART?
    - if there is gap between RVI Dx and initiation of regimen ask the reason for delay of initiation of ART
  - What was the baseline and current CD4 count and viral load?

- e.g. a known RVI pt for the past 10 years on TDF + 3TC+ DTG/EFV with baseline and current CD4 count of 250 and 500 cells/mm^3 respectively. and current viral load of 50 copies/ml
- If regimen was changed in between ask the reason of shifting to other regimens (drug side effect, treatment failure...)
- Adherent or not
- Where was the follow up and frequency of follow up

- Clinical features are Variable depending on the degree of immunodeficiency (clinical stage of disease).
- The first few weeks after initial infection, individuals may be asymptomatic or an influenza-like illness including fever, headache, rash or sore throat.
- **Acute HIV syndrome** → 50 - 70% of persons with HIV infection experience an acute clinical syndrome approximately 3 - 6 weeks after primary infection. Usually persists for 1 to several weeks
- **General symptoms** → Fever, Pharyngitis, Lymphadenopathy (70% of cases), Headache/retro-orbital pain, Arthralgias/myalgia, Lethargy/malaise/, Anorexia/Weight loss/Nausea/Vomiting/Diarrhea
- At advanced immunodeficiency, patients are at a very high risk of being infected with OI. So, write hx of opportunistic infection….
- For this section let us see hx of oesophageal candidiasis. *(for Cryptococcal meningitis & TB, look at under respective topic in long cases of Nitsibin)*

Oesophageal candidiasis hx

- Odynophagia or dysphagia
  - Scraping type of retrosternal pain during swallowing solid foods and/or fluid diet
  - Relieving and aggravating factors
  - Radiation
- Loss of appetite
- Nausea, Vomiting (characterize vomiting)
  - **Non bilious**/bilious
  - **Non projectile**/ projectile
  - **Non blood tingled**/ blood mixed
  - **Non foul smelling** / foul smelling
  - Vomiting of ingested matter
  - Frequency of vomiting (x-y days per day)
- Hematemesis and/or melena
- Diarrhoea (characterize diarrhoea)
  - Large volume
  - Watery
  - Associated abdominal pain
- Easy fatigability
- Fever (characterize fever)
  - Low/ high grade
  - Intermittent/ continuous

- Associated with chilis rigor or not

Risk factors For RVI exposure

- MSP
- Blood transfusion
- IV drug abuse (sharing of needle)
- Sharing of needle, blade and other sharp materials
- Occupation → prostitute
- MTCT (mother to child transmission)

Complication

- OI
  - ✓ TB → Pulmonary/extra pulmonary TB
  - ✓ PCP
  - ✓ Cryptococcal meningitis
  - ✓ Toxoplasmosis
- Every system Involvement
- IRIS

Sample history

Sample hx of a patient with the dx of Stage IV RVI + Disseminated TB to the lung and pleura + anemia of chronic illness

Chief compliant

Cough of one-month duration.

HPI

This is a known RVI patient for the past 04 years initially on TDF + 3TC + EFV for 03 years later the regimen changed to TDF + 3TC+ DTG when DTG was introduced to the market, with unknown baseline CD4 count and current CD4 count of 50 cells/mm^3 with current viral load of 150 copies/ml. He discontinued his follow up from UOG hospital and his medications 07 months back, because of the current pandemic (covid -19), financial and transport problem, since he lives in very remote area from gondar town.

Currently presented with cough of a month duration which is non position dependent productive cough with Mucoid, non-position dependent, Non blood tingled, non-foul-smelling sputum of 2 - 3 Arabic coffee cup per day that increase in frequency and amount progressively. Associated with this he also experienced low grade intermittent fever, Night sweet and significant weight loss from 61 kg to 53 kg which is 13% of his initial body weight.

Two weeks before admission, he also developed a gradual onset of dyspnea while doing ordinary activities like going to church which progressively increase in severity and he began to experience shortness of breath at rest within 01 week duration associated with Sudden, sharp, stabbing and localized Chest pain which is aggravated by deep breathing, coughing, sneezing, laughing and relieved by lying down on right lateral decubitus position.

- He has blurring of vision, easy fatigability and light headedness but no Tinnitus or vertigo *(anaemia in RVI from AZT toxicity, OI/B19, TB/, opportunistic malignancy with bone marrow suppression like lymphoma, anaemia of chronic illness and RVI by itself)*
- No hx of contact with a known TB patient or previous TB treatment *(RVI-TB association is very cmn OI)*
- There is no swelling over the neck, axilla or groin area *(PGL/Persistent generalized LAP/, lymphoma especially NHL)*
- He has dyspnoea but no orthopnoea, PND or palpitation *(HIV cardiomyopathy, constrictive pericarditis)*
- No hx of Flank pain, dysuria, haematuria, frequency or urgency *(TDF toxicity, HIVAN/HIV associated nephropathy/)*
- No hx of rash over the body, skin ulceration, joint pain, muscle pain or itching sensation *(skin rash of RVI /PPE, VZV…/)*
- No hx of Eye pain or discharge *(uveitis, retinitis)*
- No hx of Diarrhoea, abdominal pain, weight loss or fever *(unexplained chronic Diarrhoea > 1 month, weight loss and fever are stage III features of RVI)*
- No hx of headache, forgetfulness, visual disturbance, sleep disturbance, or Abnormal body movement *(ADC/AIDS dementia complex/, CNS toxoplasmosis, primary CNS lymphoma, HIV encephalopathy, aseptic meningitis, PMLE/progressive multifocal leukoencephalopathy/)*
- No hx of smoking or chronic alcohol intake (increased risk for respiratory disease like PCP)
- No self or family hx of DM, HTN or Asthma

Finally, he was admitted to our hospital walking by himself

Physical examination (pertinent findings)

1 **GA** → CSL

2 **Vital signs**

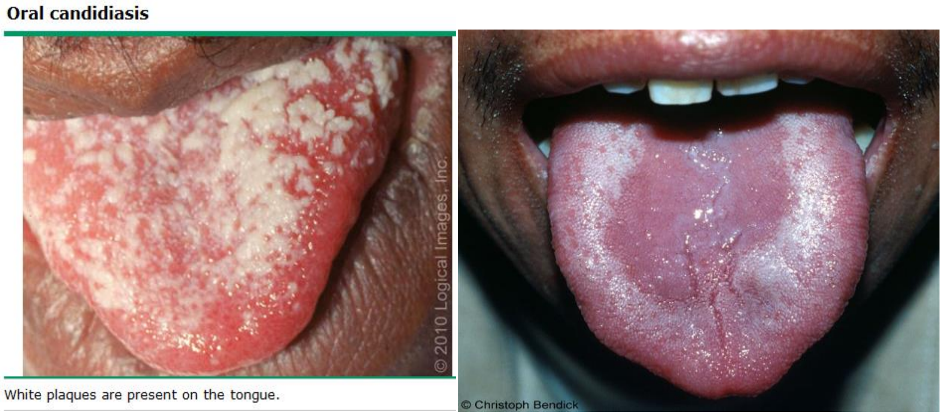
- OHT (orthostatic hypotension) from autonomic dysregulation
- Tachycardia, febrile
- emaciated

3 **HEENT**

- whitish plaque on tongue, buccal mucosa or Vertical folds on lateral lingual margin → OHL (Oral hairy leucoplakia), oropharyngeal candidiasis

N.B

OHL	Oropharyngeal candidiasis
➢ Can't be scraped by scapula ➢ Vertical folds on lateral lingual margin ➢ Caused by EBV	➢ Can be scraped by scapula ➢ Flat, painless, white cheesy plaques on the medial tongue surface ➢ Caused by C. albicans


Oral candidiasis

White plaques are present on the tongue.

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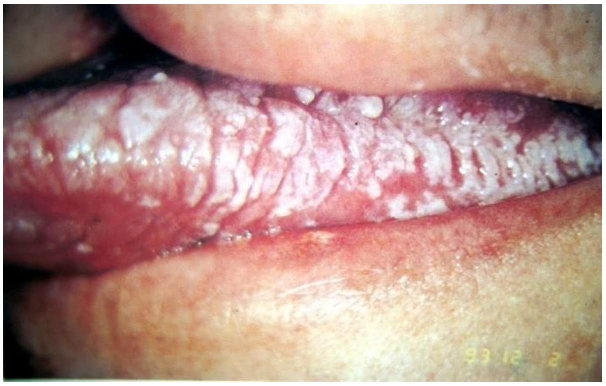
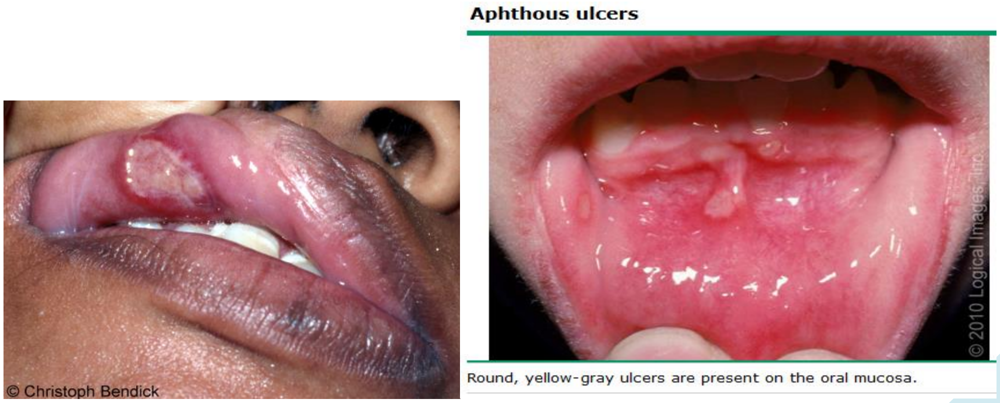
Pictures; left) Pseudomembranous thrush, right) Atrophic thrush


Picture; Oral hairy leucoplakia

- KS (Kaposi sarcoma in oral cavity)
- Aphthous ulcer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Aphthous ulcers

Round, yellow-gray ulcers are present on the oral mucosa.

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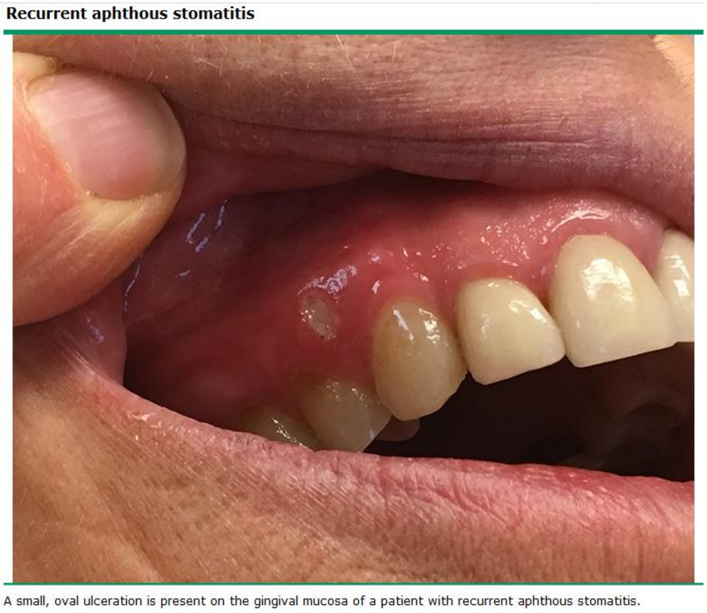
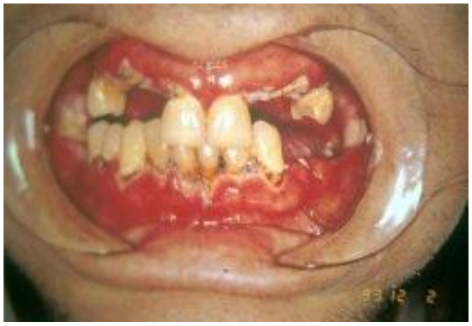
Picture; Aphthous stomatitis/ aphthous ulcer



Recurrent aphthous stomatitis

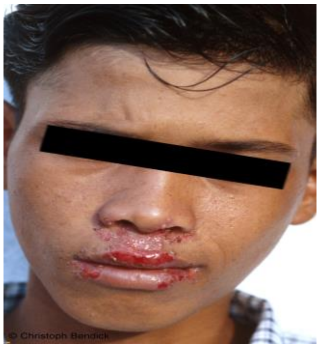
A small, oval ulceration is present on the gingival mucosa of a patient with recurrent aphthous stomatitis.

- Necrotizing Gingivitis



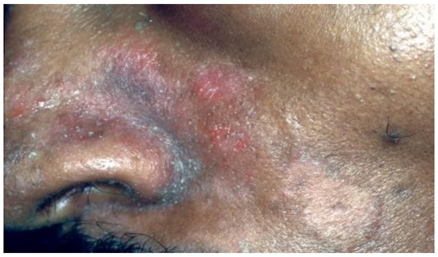
Picture; Necrotizing Gingivitis

- Periorbital edema due to HIVAN (HIV associated nephropathy)
- Eye discharge → uveitis, retinitis from CMV infection
- Retinal cotton wool spot on fundoscopy
- **Herpes labialis**
  - Shallow, **clustered ulcers** (Usually **painful)** around oral and peri oral area are characteristic
  - May be solitary and deep in the severely immunocompromised patient



Image; herpes labialis

- **Seborrheic dermatitis;** Itchy scaly skin condition, especially affecting scalp, face, upper trunk (also common in non-HIV)



Picture; Seborrheic dermatitis

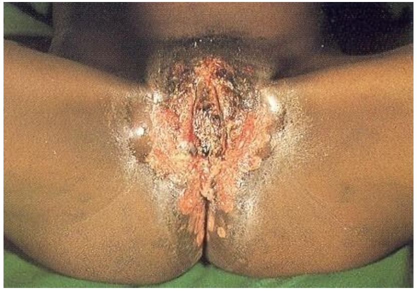
4 LGS

- PGL (persistent generalized lymphadenopathy)
- LAP from hematologic manifestation of HIV (thrombocytopenia)

5.RS

- Consolidation → pneumonia (PCP, S. pneumonia, K. pneumonia)
- Pleural effusion → Disseminated TB to pleura, NHL (primary effusive lymphoma), Pneumonia with parapneumonic effusion

6. CVS
    - CHF 2ry to DCMP (ZDV, RVI by itself)
7. **Abdominal examination**
    - HSM (hepatosplenomegaly) → hematologic malignancy like NHL, ARS (acute retroviral sxx) Phase of RVI
8. GUS
    - Genital ulcer (genital herpes)



Picture; Chronic extensive genital HSV

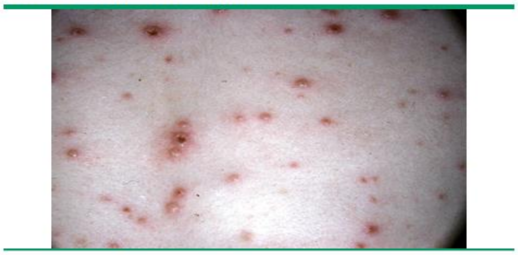
- Renal failure → HIVAN
- Hypogonadism

9. MSS
    - Leg edema → HIV cardiomyopathy resulting CHF, renal failure due to HIVAN

10. IS

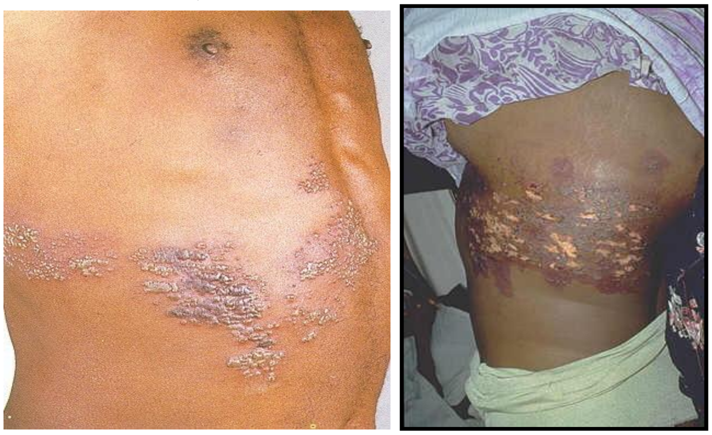
- Varicella (Chicken pox) rash

Primary varicella lesions

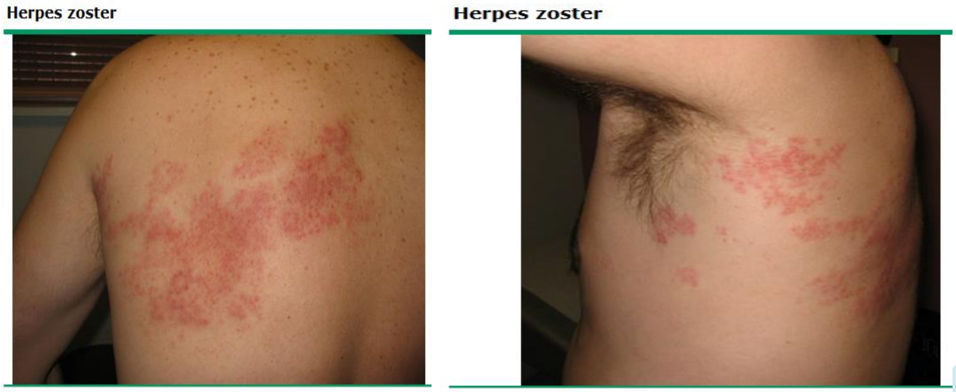


Vesicular lesions on an erythematous base are characteristic of chickenpox. The lesions occur in crops and are present in a variety of stages from maculopapular to vesicular or even pustular. Central necrosis and early crusting is also visible.

- Herpes zoster(shingles) rash
    - **Painful vesicular rash in a dermatomal distribution of a nerve supply that does not cross the midline.**
    - **Most common areas: trunk, particularly the flanks, and forehead.** Can involve the eye and cause corneal scarring and blindness.
    - **The rash is generally limited to one dermatome**, **but can occasionally affect two or three neighboring dermatomes**.
    - Some patients can also have a few scattered vesicles located at some distance away from the involved dermatome.
    - Pain sometimes comes before the appearance of the rash.
    - Vesicles form in groups and progress to crusted lesions after a few days.



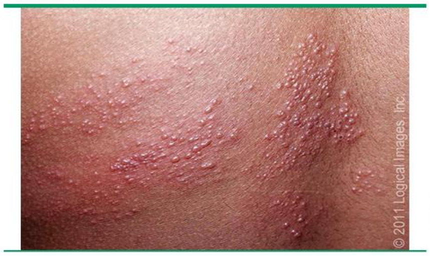
Pictures; herpes zoster infection which follows dermatomes over the chest



Herpes zoster **Herpes zoster**

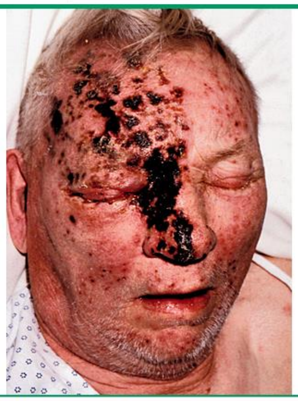
Picture;left) Herpes zoster over the left posterior chest. Right) left lateral side of the same patient

Herpes zoster



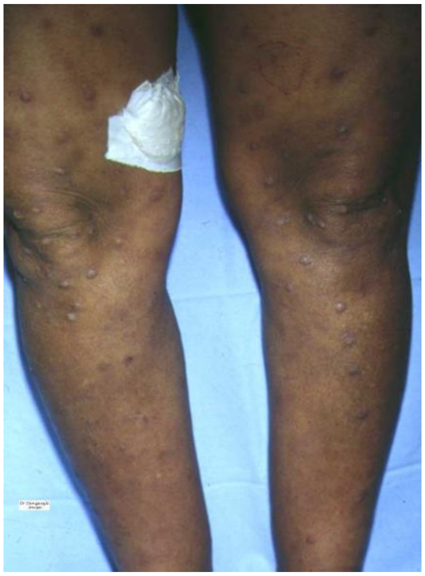
Grouped vesicles and underlying erythema are present in a dermatomal distribution.

Herpes zoster ophthalmicus



The lesions of herpes zoster progress through stages, beginning as red macules and papules that, in the course of 7 to 10 days, evolve into vesicles and form pustules and crusts (scabs). A common site is the distribution of the opthalmic division of the trigeminal nerve.

- Mucocutaneous ulcer
- Erythematous maculopapular rash of PPE (Pruritic papular eruption)
    - Intensely pruritic, discrete, firm papules with variable stages of development and predilection for extremities, though it can involve trunk and face.
    - Excoriation results in pigmentation, scarring and nodules



Picture; PPE, **Always exlcude scabies, insect bites**

Look at cutaneous OI section below for more about varicella and zoster, PPE (click here → Cutaneous disorders related to RVI infection)

11. NS

- GCS & MMSE
    - Altered mentation 2ry to ADC
- CN → CN palsy like visual disturbance

  - C. meningitis
  - Rarely toxoplasmosis
- Motor
  - FND (e.g. hemiplegia) → space occupying lesions like primary CNS lymphoma
  - Multiple lesions from CNS toxo, tuberculoma
- Sensory
  - TM (Transverse myelitis with distinct sensory level)
  - Paraesthesia
- Coordination, gait and drift
  - Impaired rapid alternation movement
  - Ataxia
  - Seizure→ encephalopathy, CNS toxoplasmosis, C. Meningitis and other aetiologies of meningitis, primary CNS lymphoma, PMLE
- Meningeal irritation sign +ve in
  - C. meningitis
  - Aseptic meningitis
  - Syphilitic meningitis
  - Lymphomatous meningitis
  - HIV meningoencephalopathy
  - PMLE (progressive multifocal leukoencephalopathy)

DDX

RVI - TB DDX for pulmonary effusion

1) Pneumonia with parapneumonic effusion
   - ✓ If infected it will form empyema
2) Primary effusive lymphoma
   - ✓ a.k.a body cavity lymphoma
   - ✓ Caused by KSV, EBV
3) Kaposi sarcoma of respiratory tract
   - Manifest with fever, cough, haemoptysis, SOB, chest pain
4) Bronchiectasis
   - Cough and mucopurulent, tenacious, position dependent, massive sputum last for months to years, hemoptysis
   - Crepitation and rhonchi
   - 2ry to
     - Acquired → TB (common in our setup), pneumonia, obstruction of the bronchial tree
     - Congenital → Cystic Fibrosis (common in westerns)
5) Fungal infections
   - ✓ Disseminated candidiasis to the respiratory tract

  - Cryptococcus
  - Histoplasmosis
  - Aspergilloma

6) Bronchogenic ca → Family hx, Smoking hx, Bloody sputum (Haemoptysis)
7) Lung Abscess
    - Offensive foul-smelling sputum which is copious in amount
    - Fever
    - If rupture → Bronchopleural fistula → effusion

RVI - esophageal candidiasis DDX

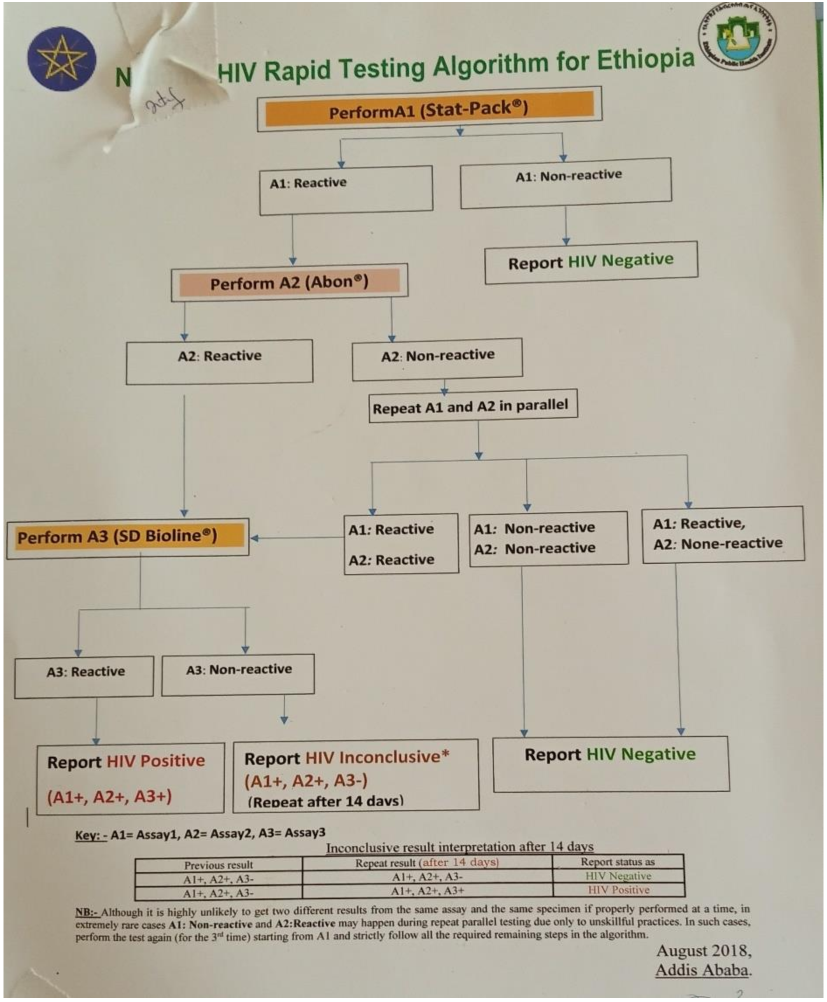
1) Esophageal candidiasis
    - AIDS Defining disease
    - Occur when CD4 count is < 200
    - N.B. AIDS defining Diseases include
        - Kaposi Sarcoma
        - Cervical ca
        - OHL
        - Cerebral toxo
        - Esophageal ca
        - ADC
2) Infectious esophagitis
    - CMV → Fever, odynophagia, substernal chest pain, nausea
    - HSV → odynophagia and/or dysphagia, fever, retrosternal chest pain, coexisting herpes labialis
3) Drug induced esophagitis
    - Characterized by severe dysphagia to the extent difficulty of swallowing saliva
4) Lymphoma to esophagus
    - Lymphoma
    - MALToma
5) Esophageal ca
6) Esophageal stricture

IX

General Ix for all RVI pt

1. **CD4 and Viral load** (Normal CD4 count = 700 - 1200 cells/μl)
    - Diagnosis of RVI include
        - Direct detection of the virus
            - **Viral load** → commonly done in our set up
            - P24 antigen
        - Antibody detection
            - **Rapid Antibody test** → commonly done in our set up

- Currently **Stat pack → Abon → SD bioline** (previously it was KHB → stat pack → unigold)


N
HIV Rapid Testing Algorithm for Ethiopia
PerformA1 (Stat-Pack®)
A1: Reactive
A1: Non-reactive
Report HIV Negative
Perform A2 (Abon®)
A2: Reactive
A2: Non-reactive
Repeat A1 and A2 in parallel
Perform A3 (SD Bioline®)
A1: Reactive
A2: Reactive
A1: Non-reactive
A2: Non-reactive
A1: Reactive,
A2: None-reactive
A3: Reactive
A3: Non-reactive
Report HIV Positive
(A1+, A2+, A3+)
Report HIV Inconclusive*
(A1+, A2+, A3-)
(Repeat after 14 days)
Report HIV Negative

Key: - A1= Assay1, A2= Assay2, A3= Assay3

Inconclusive result interpretation after 14 days

Previous result	Repeat result (after 14 days)	Report status as
A1+, A2+, A3-	A1+, A2+, A3-	HIV Negative
A1+, A2+, A3-	A1+, A2+, A3+	HIV Positive

NB:- Although it is highly unlikely to get two different results from the same assay and the same specimen if properly performed at a time, in extremely rare cases **A1: Non-reactive** and **A2:Reactive** may happen during repeat parallel testing due only to unskillful practices. In such cases, perform the test again (for the 3rd time) starting from A1 and strictly follow all the required remaining steps in the algorithm.

August 2018,
Addis Ababa.

- ELISA
- Western blot

2. CBC→ Megaloblastic anemia from AZT toxicity, pancytopenia
3. RBS
4. U/A → proteinuria in HIVAN
5. CXR
    - r/o TB, pneumonia
    - PCP → perihilar infiltrate, ground glass appearance
6. Sputum examination (gene x-pert for TB screening)

- **Gram stain** from BAL, induced sputum, Transbronchial biopsy→ definitive dx for PCP
- **AFB**
- **Culture**
- **Gene x-pert**
- **PCR**

7. RFT → for drug toxicity, HIVAN
8. LFT → for drug toxicity
9. Lipid profile (Triglyceride, Cholestrol, HDL and LDL)
10. Hepatitis screening → before initiation of ART since HBV also treated with TDF

RVI TB Ix → the above baseline IX plus

11. CXR
    - TB features on CXR
        - o Early typical adult features
            - ☛ Upper lobe infiltration/cavitation
            - ☛ No significant LAP/ pleural effusion
    - ✓ Late atypical features
        - o Lower/middle lobe opacity
        - o Little/no cavitation
        - o Miliary/interstitial pattern
        - o Hilar/paratracheal LAP
        - o Pleural/pericardial effusion
        - o May be normal finding
13. Pleural fluid analysis → refer under short cases of Nitsbin (click here → pleural fluid analysis)
12. Chest U/S → can differentiate
    - ✓ Loculated effusion from tumor
    - ✓ Pleural effusion from pleural thickening
13. Chest CT → also differentiate pleural effusion from pleural thickening
14. Culture → gold standard Ix in RVI-TB
15. RFT and LFT for Anti TB toxicity

N.B

if you suspect esophageal candidiasis in RVI patient there is no specific investigation modality. Rather, treat with systemic antifungals and if odynophagia improves within 3-4 days, the cause of odynophagia is highly likely esophageal candidiasis

Other Ix based on indication

16. Brain CT and MRI → can show us ring enhancing lesion in CNS toxoplasmosis
17. Abdominal U/S → CKD from HIVAN

Laboratory monitoring for toxicity of ART

- ❖ Baseline
    - ✓ CBC
    - ✓ Liver enzymes

  - ✓ RFT
  - ✓ RBS
  - ✓ Pregnancy test
  - ✓ Lipid profile

- ❖ Follow up
  - ✓ Baseline Ix Repeated monthly (particularly at the initiation of ART) then every 3 months once stabilized. Then at any time if indicated

Discussion

5.1 HIV/AIDS

- **HIV (***Human Immuno-deficiency Virus)* **is** an infectious disease caused by HIV, a human retrovirus
- It is essentially a disease of the immune system, which results in progressive immunodeficiency state leaving the individual susceptible to various types of infections and the development of malignancies.
- HIV disease should be viewed as a spectrum ranging from primary infection, with or without the acute syndrome, to an asymptomatic stage, to advanced disease characterized by profound immunodeficiency and susceptibility to opportunistic infections (OI).
- The most advanced stage of HIV infection is called **AIDS**
- **AIDS** (Acquired Immunodeficiency Syndrome) is the late /most advanced/ stage of HIV infection
- **Current case definition for AIDS**;
- ☛ Any HIV-infected person with a $CD4^+$ T-cell count <200/µl
- ☛ Development of an AIDS-defining clinical condition (see staging below)

Etiology

- **Human retroviruses; HIV-1 and HIV-2**
  - ✓ Family of human retroviruses (Retroviridae), Subfamily of lentiviruses
  - ✓ RNA viruses whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase
- HIV-1 is the most common cause of AIDS worldwide.
- HIV-2 has been identified predominantly in western Africa but Small numbers of cases have also been reported in Europe, South America, Canada, and the U.S. Has ~40% sequence homology with HIV-1 and More closely related to simian immunodeficiency viruses

Transmission

- ❖ **Sexual contact (unsafe):** heterosexual and homosexual. It is major means of transmission.
- ❖ **Contact with blood, blood products, or other bodily fluids** (as in drug abusers who share contaminated intravenous needles)

    - Potentially infectious fluids
        - **Blood, Seminal fluid, Vaginal secretion**
        - **Body fluids:** CSF, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid.
        - **Breast milk, Pus**
    - BUT, Saliva, Tear, Sweat, Vomitus, Sputum, Nasal secretion, Stool &Urine are not considered potentially infectious unless they are visibly bloody.
- **MTCT**/Mother to child transmission/; Intrapartum or perinatally from mother to infant or via breast milk
- **Contact with HIV-infected specimens** (a definite but small occupational risk of infection for health care workers and laboratory personnel)

- STIs- play a role in HIV disease transmission and progression

Diagnostic Approach

- Diagnosis of HIV infection → Diagnosis depends on demonstration of antibodies to HIV and/or direct detection of HIV or one of its components. **Antibodies to HIV appear 2 - 12 weeks after infection**
- Diagnosis of AIDS → CD4+ T-cell count <200/µL or AIDS-defining clinical condition

Effects of HIV

- Direct effects:
    - ✓ Nervous (encephalopathy and peripheral neuropathy)
    - ✓ Kidney (HIVAN = HIV-associated nephropathy)
    - ✓ Cardiac (HIV cardiomyopathy)
    - ✓ Endocrine (hypogonadism in both sexes)
    - ✓ GI tract (dysmotility and malabsorption/ ?HIV enteropathy)
- Indirect effects:
    - ✓ **Opportunistic infections and tumors** as a consequence of immunosuppression

Natural history of HIV infection

1. **Phase 1: Transmission**
2. **Phase 2: Acute retroviral syndrome**
    - ✓ IP - 2-6 weeks post exposure
    - ✓ Present with Fever, Sore throat, Nausea /Vomiting/diarrhea, Weight loss /myalgia /arthralgia, **Maculopapular rash** (face, trunk, extremities), Hepatosplenomegaly, Neurologic abnormalities (**Aseptic meningitis**, Encephalitis, Peripheral neuropathy, **GBS,** Facial Palsy, Brachial neuritis, Psychosis
    - ✓ HIV Ab test negative

- ✓ CD^{+}_{4} T cells number and function decline; But high viremia, high HIV RNA levels and P^{24} antigenemia (high viral load) …
- ✓ Period of extreme infectiousness
- ✓ Be aware of false negatives
- ✓ Using rapid tests >95% of patients will test positive within 6 months

3. Phase 3: **HIV Sero-conversion (Window Period)**
   - ✓ **Window period is a time period between acquisition of HIV infection and antibody production**
   - ✓ **Sero-conversion usually occurs within 6 weeks (**80% antibody +ve**) to 3 months** (100% antibody +ve) after transmission. Rare cases will take longer
4. Phase 4: Latent infection (**Clinical latency**)
   - ✓ Asymptomatic stage
   - ✓ No virologic latency → i.e. Period of continued viral replication and gradual decline in $CD_4{}^{+}$ cells
   - ✓ **Viral set point:**
     - The level of HIV viremia early in the course of HIV where the viral load plateaus
     - predicts the likelihood of progression to AIDS in the next 5 years (The higher the viral set point: The more rapid disease progression to AIDS and the more rapid the fall in CD4 count)
   - ✓ In contrast to viral load, baseline CD4 is not a good predictor of time to progression to AIDS. However, as the CD4 count declines over time (50-100/year), patients will develop opportunistic infections

5. **Phase 5: AIDS**

CDC classification system of HIV-infected persons

CD 4 cell count	A (asymptomatic, PGL, acute retro viral syndrome)	B (symptoms not in A or C)	C (AIDS indicators)
> 500 cells/μl	A1	B1	C1
200 - 499 cells/μl	A2	B2	C2
< 200 cells/μl	A3	B3	C3
A3, B3 and C (C1 - C3) defines AIDS			

N.B for clinical practice, WHO classification is used commonly and CDC classification is not used most of the time.

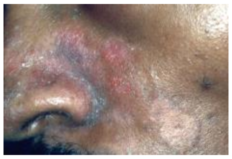
Patterns of HIV Disease Progression from primary HIV infection

1) Typical Progressors (90%) → 7 - 10 years
2) Rapid Progressors (< 5%) → <3 years

- ☛ High viral load, faster CD^{+}_{4} decline

3) Long-term Non-progressors (< 10%) → >15-20 years
    - ☛ Normal /stable CD4, without ART

Clinical Stages of HIV Disease as per WHO Classification

Stage	Features	Performance Status
1	≥1 of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection; ➢ **Asymptomatic** HIV infection ➢ **Persistent generalized lymphadenopathy (Enlarged lymph nodes > 1cm, in 2 or more non-contiguous extra-inguinal sites, in absence of known cause; lasting more than 3 month)** ➢ ARS (Acute Retroviral /HIV/Syndrome) → Acute (primary) HIV infection with accompanying illness or history of acute HIV infection	**asymptomatic, normal activity**
2	➢ **Unexplained Weight loss** <10% of presumed body weight ➢ **Minor mucocutaneous** manifestations: ✓ Papular pruritic eruptions (PPE) ✓ Seborrhoeic dermatitis ✓ Angular chelitis ✓ Fungal nail infections of fingers ✓ Recurrent oral ulcerations (≥ 2 times/6months)  Picture; **Seborrhoeic dermatitis;** Itchy scaly skin condition, especially affecting scalp, face, upper trunk (also common in non-HIV) ➢ **Herpes zoster** (current or in last 5 years) ➢ Recurrent **upper respiratory tract infections** (sinusitis, otitis media, bronchitis, pharyngitis)	**symptoms, but nearly fully ambulatory**
3	➢ **Oral candidiasis** ➢ **Unexplained Weight loss** >10% ➢ **Unexplained chronic diarrhoea > 1 month** ➢ **Unexplained prolonged fever** (intermittent or constant for >1 month) ➢ **Recurrent vaginal candidiasis** ➢ **Oral hairy leucoplakia (OHL)** ➢ **Pulmonary tuberculosis** currently or within the previous 2 years ➢ **Severe presumed bacterial infections** (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) ➢ **Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis** ➢ Unexplained: ✓ Anaemia (<8g/dl) or ✓ Neutropenia (<500/mm³) or ✓ Thrombocytopenia (<50,000/mm³) for > 1 month	**In bed more than normal but < 50% of normal daytime during the previous month**
4	➢ **Recurrent severe bacterial pneumonia** ➢ **Chronic HSV infection- orolabial, genital, or anorectal of > 1 month duration** ➢ **CMV infection (other than liver, spleen, LN)** ➢ **CNS toxoplasmosis** ➢ **Cryptococcal meningitis (or other extra pulmonary crypto)** ➢ **Extrapulmonary tuberculosis** ➢ **HIV encephalopathy** ➢ **Progressive multifocal leukoencephalopathy (PML)**	**In bed > 50% of normal daytime during previous month**

	➢ **HIV wasting syndrome** ✓ Weight loss > 10% **PLUS** ✓ Unexplained chronic diarrhoea > 1 month **OR** ✓ Unexplained prolonged fever > 1 month ➢ **Pneumocystis pneumonia (PCP)** ➢ **Candidiasis of esophagus, trachea, bronchi, or lungs** ➢ **Any disseminated endemic mycosis (Histoplasmosis, Coccidiomycosis, Penicilliosis)** ➢ **Kaposi's sarcoma** ➢ **Invasive cervical carcinoma** ➢ **Cryptosporidiosis, Isosporiasis** ➢ **Disseminated Mycobacterial diseases other than tuberculosis** ➢ **Recurrent non-typhoidal salmonella septicaemia (≥ 2 episodes in 1 year)** ➢ **Lymphoma (cerebral or B-cell NHL)** ➢ **VL** ➢ **Visceral Herpes simplex** ➢ **HIVAN (HIV - associated nephropathy)** ➢ **HIV - associated cardiomyopathy** ➢ **HIV Enteropathy**	

T- staging

- T-staging refers to clinical staging while on ART for at least 6 months
- Based on T-staging WHO stage 1 corresponds to stage T1, Stage 2 to T2, stage 3 to T3 and Stage 4 to T3
- Used as an indicator of treatment outcome
- Prompts consideration to switch therapy
- Clinical events before the first six months of therapy are excluded from this definition

5.2 Treatment of RVI

Objective

- Suppress viral replication to undetectable levels durably;
- Restore and preserve immunologic function;
- Prevent HIV transmission;
- Prevent opportunistic infections;
- Rehabilitate the patient and allow full function and survival.

Non pharmacologic

- Counseling and psychological support
- Nutritional support
- Socio-economic support

Pharmacologic

- Management of HIV disease includes prevention and treatment of OI and controlling viral replication with HAART.

Goal of HAART

- Virological → to decrease viral load
- Immunological → to increase CD_4 Cell count (Immunity)
- Clinical → to decrease occurrence of OI

} **Healthy life style**

Indications for initiation of ART

General Considerations for ART:

- Effectiveness of ART is assessed by clinical observations, CD4 cell count and viral load.
- ART should be initiation ASAP and not delayed until the immune system is irreversibly damaged.
- For ART naïve patients, treatment is initiated with a combination of 3 medicines (**Triple Therapy**); consisting of 2 NRTIs and a 3rd medicine from the NNRTI, Integrase Inhibitor (II) or Protease Inhibitors (PI).

Table: Anti-retroviral medicines for adults and adolescents

Medicine class/Medicine	Dose (most of the time found in FDC form)	Common side effects*
Nucleoside & Nucleotide RTI's (NRTI)		
Tenofovir (TDF)	300 mg daily	**Nephrotoxicity**
Lamivudine (3TC)	150 mg BID or 300 mg daily	**Safe drug among ART**
Zidovudine (ZDV, AZT)	250–300 mg BID	**Megaloblastic anemia**
Abacavir (ABC)	300 mg BID or 600 mg daily	Hypersensitivity reaction
Emtricitabine (FTC)	200 mg daily	**Safe,** may cause Headache, diarrhoea, rash
Stavudine (D4T)		Peripheral neuropathy, **lipoatrophy**
Didanosine (ddI)		Pancreatitis
Non-Nucleoside RTI's (NNRTI)		
Efavirenz (EFV)	400-600mg daily	CNS toxicity, rarely severe skin reaction
Nevirapine (NVP)	200 mg daily for 14 days, then 200mg BID	**Drug-Drug interaction with Rifampicin**, Hepatitis, Hypersensitivity reaction
Etravirine (ETV)	200 mg BID	
Protease inhibitors (PI)		
Atazanavir/ritonavir (ATV/r)	300mg/100mg daily	Headache, diarrhoea,rash
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg daily (for individuals with	

	no previous PI) or 600 mg + 100 mg BID (for individuals with previous PI use)	
Lopinavir/ritonavir (LPV/r)	➢ 400mg/100mg BID (533mg/133mg BID when combined with EFV or NVP ➢ Considerations for individuals receiving TB therapy ➢ In the presence of rifabutin, no dose adjustment required. ➢ In the presence of rifampicin, adjusted dose of LPV/r: LPV 800 mg + RTV 200 mg BID or LPV 400 mg + RTV 400 mg BID). OR, SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.	➢ Lopinavir → Paresthesia, hyperlipidemia ➢ Ritonavir → Hyperglycemia, asthenia
Integrase inhibitors / Integrase strand transfer inhibitors (II / INSTIs)		
Dolutegravir (DTG)	50 mg daily, If TB coinfection, 50mg BID	
Raltegravir (RAL)	BID	
*The major causes of drug discontinuation in the first 3-6 months after initiating ART are due to drug toxicities *Toxicities of NNRTIs (NVP and EFV) occur in the first few weeks, and may be life-threatening *ABC hypersensitivity reaction starting from first week following initiation *Anaemia and neutropenia due to ZDV occur in the first 3 months		

When to start treatment

- Unlike the previous recommendations, **it is critical to initiate ART ASAP (same day to within 7 days of HIV diagnosis);** this reduces HIV related morbidity and mortality, and reducing forward transmission of HIV including MTCT.
- **All HIV positives people are eligible for ART** irrespective of their WHO clinical staging and/or CD4 count following a confirmed HIV diagnosis, clinical assessment and assessment of client readiness.
- As a priority, ART should be initiated ASAP in all adolescents and adults with advanced disease (WHO stage 3 to 4, CD4 count ≤350 cells/mm3) and all children regardless of WHO staging and CD4 count/percentage
- For women identified at labor and delivery, provide ART with in the same hour of HIV diagnosis with brief counseling and provide detailed counseling on ARV and adherence after delivery.
- Requirements for initiation of ART
  - ☛ HIV positive test result with written documentation
  - ☛ Start only patients with medical **eligibility for ART**
  - ☛ **Ensure readiness** of patient for ARV therapy
- Infections may cause transient decrease in CD4 count & be careful with interpretation of the CD4 count. Therefore, **treat and stabilize any OIs before**

starting ART.

Medicine Regimens

First-line regimens for adults and adolescents: for treatment naive patient for the first time.

- TDF + 3TC + DTG/EFV as a once-daily dose.
    - ✓ FDC (Fixed-dose combinations) and once-daily regimens are preferred.
    - ✓ For HIV/TB co-infected adults and adolescents, the recommended dose of DTG is 50 mg twice daily.

Table Summary of first-line ART regimens for adults, pregnant & breastfeeding women, adolescents and children.

Population	**Preferred first-line regimens**	**Alternative first-line regimens** [a]
Adults (including those with TB/ HIV [b]-coinfection)	➢ TDF + 3TC + DTG (FDC)* OR ➢ TDF + 3TC + EFV (FDC)**	➢ AZT + 3TC + EFV/NVP OR ➢ TDF + 3TC + NVP
Pregnant and breastfeeding women	➢ TDF + 3TC + EFV (FDC)	
Adolescents (10 to 19 years) weight ≥35 kg (Including those with TB/HIV [b]-coinfection.)	➢ TDF + 3TC + DTG (FDC)* OR ➢ TDF + 3TC + EFV (FDC)**	➢ AZT + 3TC + EFV/NVP OR ➢ TDF + 3TC + NVP OR ➢ ABC + 3TC + EFV
Children 3 years to <10 years and adolescents' weight <35 kg	➢ AZT/ABC + 3TC + EFV	➢ AZT + 3TC + NVP OR ➢ TDF + 3TC + EFV OR ➢ TDF + 3TC + NVP OR ➢ ABC + 3TC + NVP***
Children <3 years	➢ ABC/AZT + 3TC + LPV/r	➢ ABC/AZT+ 3TC + NVP

[a] *ABC or boosted PIs (ATV/r, LPV/r) can be used in special circumstances*

[b] *In case of TB-HIV coinfection, the dose of DTG should be 50mg BID.*

**If available as triple FDC, TDF+3TC+DTG is the preferred regimen for HIV positive adult and adolescent patients.*

***TDF+3TC+EFV400 (FDC) will replace the TDF+3TC+EFV600 (FDC) for adults and adolescents (except for pregnant mothers and TB/HIV co-infected patients as there is no adequate data for this groups) up on availability.*

**** Caution: co-administration of ABC with NVP in pediatric patients will increase the risk of hypersensitivity reaction and requires extreme precaution.*

Management of advanced HIV disease

- For adults and adolescents, and children >5 years, advanced HIV disease is defined as CD4 cell count <200cells/mm3 or WHO stage 3 or 4 event.
- All children <5 years old with HIV are considered as having advanced HIV disease.
- A package of interventions including screening, treatment and/or prophylaxis for major OIs, rapid ART initiation and intensified adherence support should be offered to everyone presenting with advanced HIV disease including those who are reengaging with care after a period of interruption.

First line for advanced HIV disease treatment

- ✓ TDF + 3TC + DTG/EFV as a once-daily dose.

Alternatives first line

- ✓ AZT + 3TC + EFV

Second line drugs are used if there is treatment failure or if there is serious side effect develops from 1st line drugs.

5.2.1 Antiretroviral treatment failure

- **Routine viral load testing is a more sensitive and earlier indicator of treatment failure.**
- To detect treatment failure proactively, routine viral load testing should be done at 6 and 12 months of initiating ART and then every 12 months thereafter and plus whenever there is clinical or immunologic suspicion of treatment failure.

Table: Definitions of clinical, immunological and virologic failure for the decision to switch ART regimens

Failure	Definition	Remark
Clinical failure	**Adults and adolescents** ➢ New or recurrent clinical event indicating severe immunodeficiency (WHO clinical **stage 4** condition and **certain** WHO clinical **stage 3** conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) **after 6 months of effective treatment.**	➢ The condition must be differentiated from IRIS occurring after initiating ART.
Immunologic failure	**Adults and adolescents** ➢ **CD4 count ≤ 250** cells/mm3 following clinical failure or **Persistent CD4 levels below100** cells/mm3.	➢ Without concomitant or recent infection to cause a transient decline in the CD4 cell count. ➢ Persistent is to mean at least 2 CD4 measurements below the threshold. ➢ Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virologic failure.
	Children ➢ Younger than 5 years: ✓ Persistent CD4 level < 200 cells/mm3 or <10%; ➢ Older than 5 years: ✓ Persistent CD4 levels < 100 cells/mm3.	
Virologic failure	➢ **Viral load > 1000 copies/ml** based on **2 consecutive viral load measurements in 3 months**, with enhanced adherence support following the first viral load test.	➢ An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed. ➢ Viral Load testing should not be done when there is an acute infection/fever.

Causes of Treatment Failure

- Viral Factors:
  - drug-resistant virus, either transmitted or acquired
  - Aggressive virus: a “rapid progressor”, “syncytial forming.”
  - Patient Factors
- Patient factors (Poor adherence)
  - Poor absorption
  - Rapid elimination
  - comorbidities e.g., active substance abuse, depression
- Drug Factors
  - Low potency regimen
  - Antagonist combination
  - Drug-drug interaction
  - Drug-food interactions
  - Inappropriate dosing

- ✓ Drug side effects and toxicities

Re-engaging with care after ART interruption

- Re-evaluate for possible adherence barriers and advanced clinical conditions.
- Then resume the same (previous) ART regimen used before interruption. However, people interrupting NNRTI - containing regimen (high risk of drug resistance) should restart using a DTG - containing regimen (has high genetic barrier to resistance and can bring rapid viral suppression)
- Then, ongoing Enhanced Adherence Counseling (EAC), frequent follow-up, close viral load monitoring/determining at 3 and 6 months after resuming ART is required.
- **If there is confirmed failure of the current treatment regimen, the client needs to be switched to appropriate second-line or third line regimen.**

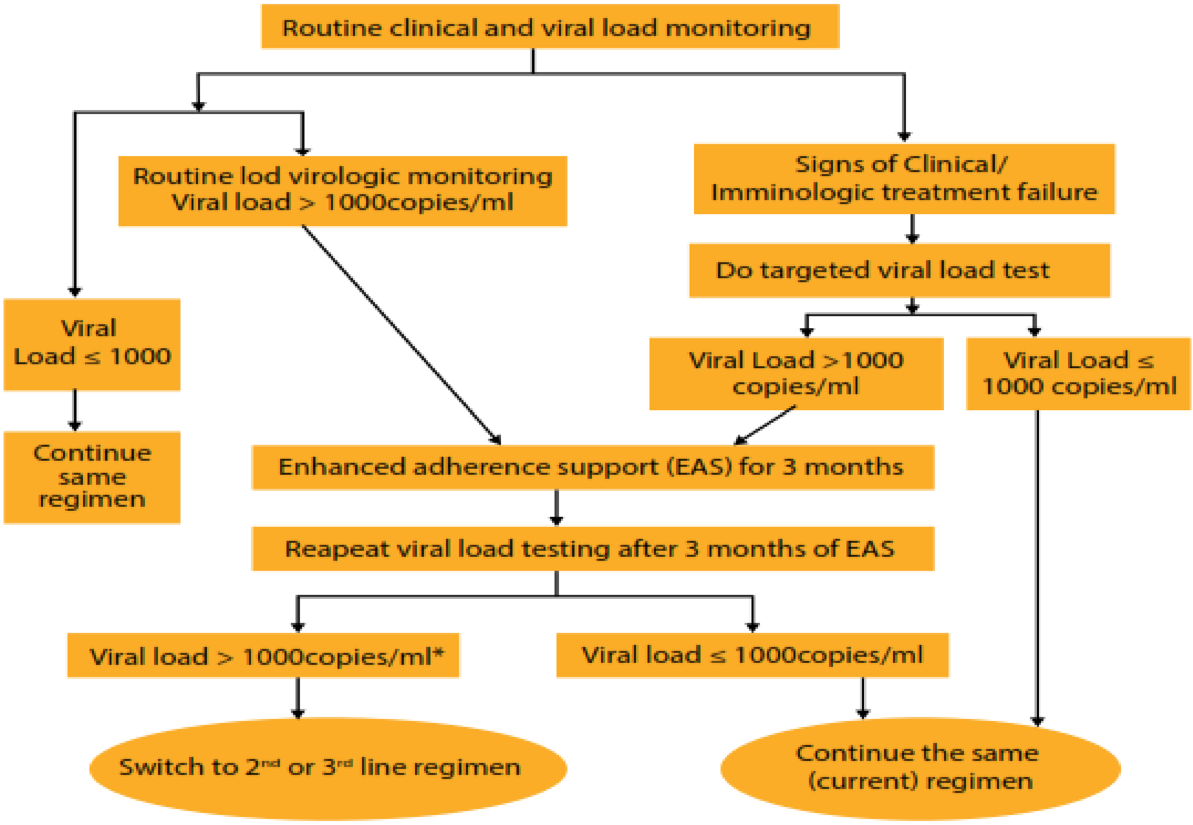

Routine clinical and viral load monitoring
Routine lod virologic monitoring
Viral load > 1000copies/ml
Signs of Clinical/
Imminologic treatment failure
Do targeted viral load test
Viral
Load ≤ 1000
Viral Load >1000
copies/ml
Viral Load ≤
1000 copies/ml
Continue
same
regimen
Enhanced adherence support (EAS) for 3 months
Reapeat viral load testing after 3 months of EAS
Viral load > 1000copies/ml*
Viral load ≤ 1000copies/ml
Switch to 2nd or 3rd line regimen
Continue the same
(current) regimen

*Figure. Algorithm for routine clinical and viral load monitoring. * For those patients with identified significant adherence barriers, it is advisable to extend the provision of Enhanced adherence counseling for 6 months before doing the second Viral load testing in order to properly address the barriers and give optimal time for viral suppression to happen*

- Using a boosted PI + two NRTI combinations is recommended as the preferred for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART.
- In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according to their age.

Table: preferred second-line ART regimens for adults and adolescents		
Target population	**Preferred second-line regimen**	
Adults and adolescents (≥10 years)*	If TDF+3TC+DTG#used in first-line	AZT + 3TC + ATV/r or LPV/r
	If AZT was used in first-line ART	TDF + 3TC + LPV/r or ATV/r
	If TDF was used in first-line ART	AZT + 3TC + LPV/r or ATV/r
HIV and TB co-infection	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily).
HIV and HBV co-infection	DTG + TDF/3TC + ATV/r OR AZT + TDF + 3TC + (ATV/r or LPV/r)	➢ If switching an ARV regimen in HBV/HIV coinfected patients, HBV active ARV drugs (TDF/3TC) should be continued in the new regimen. ➢ Discontinuation of HBV active ARV drugs may lead to reactivation of HBV and result in serious hepatocellular damage. ➢ The DTG regimen may be preferred if the loose AZT is unavailable. ➢ If DTG regimen used, watch increased hepatotoxicity of DTG and HBV

Adult clients taking ABC can be shifted to AZT.* ***For* pregnant *women same regimens recommended as for adults and adolescents, but cautious counseling or alternative suggestions (if available) is required before DTG use (low NTD risk of 0.3% vs 0.1 % in non DTG regimens).*[10] *If TDF and ABC have been used in the first-line regimen, patients may be referred to experienced physicians for selection of the second-line medicines.*

#For HIV/ TB co-infected adults and adolescents, the recommended dose of DTG is 50 mg twice daily. Children weighing more than 20 kg can take adult 50mg film-coated tablets,RAL can be used in neonates and children less than 20 kg body weight.

Identification and management of second-line treatment failure

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[10] "Start ART for HIV positive mothers who are breastfeeding even if it was not started before (currently recommended regimen TDF/3TC/ DTG)" MANAGEMENT PROTOCOL ON SELECTED OBSTETRICS TOPICS FOR HOSPITALS, 2020

- Patients who are on 2nd line regimen and have high viral load level (>1000 copies/ml) after 6 months of treatment need to go through the algorithm as described for first line treatment failure with enhanced adherence support and repeat test after 3 months to decide second line treatment failure.
- If confirmed to have 2nd line failure, consult (or refer to) experienced physicians for initiation of 3rd line regimens.
- Before switching to 3rd line regimen, ensure the following.
  - ✓ Two consecutive viral load measurements > 1000 copies/ml at least 3 months apart.
  - ✓ First viral load measurement done at least 6 months after switching to 2nd line regimen.
  - ✓ The repeat viral load test should be done after 3 months of enhanced adherence support.
  - ✓ The approach in switching to 3rd line should follow the guiding principles listed out for switching to 2nd line drugs.

5.2.2 Monitoring ARV Treatment

- Start from the day of initiation.
- The first six months of therapy are especially critical for monitoring.

What to expect in the first months of ART and how to manage them?

- ART initiation may be associated with IRIS as well as early adverse drug events, such as drug hypersensitivity, in the first three months of ART
- Be alert to OIs and/or IRIS as well as adverse drug events, in the early phase of ART initiation.
- Especially a high mortality seen in the first three to six months of ART initiation among people who started ART with advanced HIV disease with existing co-infections and/or co- morbidities, severely low hemoglobin, low body mass index (severe malnutrition) and/or very low CD4 counts.
- Failure to achieve CD4 recovery or presence of CD4 decline after treatment initiation particularly after one year (common in those with very low CD4 cell on ART initiation) should alert to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for OI such as CPT till patients recovers immunologically.

5.3 IRIS (Immune reconstitution inflammatory syndrome)

- IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART.
- It occurs among 10 - 30% of the people initiating ART, usually within the first 4 - 8 weeks after initiating therapy.
- It may present in two different ways:
  - ✓ **Paradoxical IRIS**
    - An OI or tumor diagnosed before ART initially responds to treatment but then deteriorates after ART starts
    - The most serious and life-threatening forms of paradoxical IRIS are for TB, Cryptococcus's, Kaposi's sarcoma and hepatitis.
    - BCG vaccine - associated IRIS (localized and systemic) may occur in some HIV infected infants.
  - ✓ **Unmasking IRIS** → initiating ART triggers disease that is not clinically apparent before ART.
- **It is diagnosis of exclusion.** i.e. It should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity
- Before initiating ARV, providers need to give due consideration for patients with low CD4 cell count (<50 cells/mm3) at ART initiation, disseminated OIs or tumors and a shorter duration of therapy for OIs before ART starts as they are the main risk factors for IRIS.

- **IRIS is not indicative of treatment failure or drug side effect and *doesn't need discontinuation or change of ARVs*.** It is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of or poor adherence to ART.
- (NB: Actively watch for IRIS in patients starting with first-line regimens containing integrase-inhibitors such as DTG)
- The most important steps to **reduce the development of IRIS include:**
  - ✓ Earlier HIV diagnosis and initiation of ART before a decline to < 200 CD4 cells/mm3
  - ✓ Improved screening for OIs before ART, especially TB and Cryptococcus; and
  - ✓ Optimal management of OIs before initiating ART.
- Timing of ART in people with OIs requires; balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

Investigation and diagnosis of IRIS

- Most or all of the following features should be present in order to **make the diagnosis of IRIS**:
  - ✓ A low pretreatment CD4 count (often < 100 cells/μL) except in tuberculosis. IRIS secondary to preexisting TB infection may occur in individuals with CD4 counts >200;
  - ✓ A positive immunological response to ART;
  - ✓ The absence of evidence of drug-resistant infection, bacterial super infection, drug allergy or other adverse drug reactions, patient noncompliance, or reduced drug levels due to drug-drug interactions or mal-absorption after appropriate evaluation for the clinical presentation;
  - ✓ The presence of clinical manifestations consistent with an inflammatory condition; and
  - ✓ A temporal association between HAART initiation and the onset of clinical features of illness- usually within the first 6 months.
- *Commonly seen when ART is started at very low CD4 count.*
- Atypical presentations are common
  - ✓ localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, increased intracranial pressure, uveitis, sarcoidosis, and Graves' disease.
  - ✓ The clinical course can be protracted, and severe cases can be fatal
  - ✓ Steroids may be indicated for some conditions
- Conditions that can present as IRIS: TB, cryptococcal meningitis, PCP, CNS toxo, herpes virus, CMV, PMLE, kaposi sarcoma, Grave's disease…

Management of IRIS

- Patients should generally be treated for the underlying OI ASAP.
- Continuation of ART when IRIS occurs.

Anti-inflammatory agents' vs IRIS:

- Particularly helpful in settings of obstructive mass lesions (e.g. expanding cervical lymph node).
- Their use, particularly corticosteroids, must be weighed against potential risks/side effects.
- If corticosteroids, initiate therapy with **prednisone 1 mg/kg/day** (maximal dose 60 - 80 mg) followed by a rapid **taper over a 10 to 14-day period.**
- IRIS in closed spaces (e.g. CNS OI) should be managed promptly to avert significant morbidity and mortality.

Follow up

- Standardized clinical assessment of patients and, when available **baseline CD4** count, are important to determine the severity of immunosuppression and decide on initiation of prophylactic therapies.
- Before initiating ART, patients shall be thoroughly evaluated at baseline and periodically for the rest of their lives to monitor toxicity, intolerance, poor response or failure to treatment, OIs, other co-morbidities are always need to be looked for and managed.
- Once on ART:
- ☛ **1st follow-up visit will be every 1 week for the first 2 consecutive visits and a gradual extension.**
- ☛ **Then, appointed every 2 weeks during the 1st month of treatment and**
- ☛ **Every 4 weeks (every month) then after until 24 weeks of treatment.**
- ☛ **After the 24th weeks of initiation of antiretroviral therapy patients will be scheduled to return every 12 weeks.**
- During each visit, patient should be evaluated for new symptoms that may be related to medicine side effects, the disease progression, and clinical improvements/deterioration, and adherence, development of OIs or recurrent problems that may exist
- Patients should be encouraged to come at any time if they have concerns and can be seen out of the above schedule whenever necessary.
- When a woman in reproductive age is taking DTG containing regimen, occurrence of pregnancy shall be prevented and monitored. If pregnancy happens while on DTG containing regimen, DTG shall be replaced with EFV.
- For ART, a high level of sustained adherence is extremely necessary.

Monitoring for toxicity of ART

Guiding principles

- ✓ Establish whether the clinical condition is due to ARV toxicities, other drugs, or other illness including new OI's
- ✓ Try to identify the responsible ARV drug.
- ✓ Assess the severity using toxicity grading matrix.

Clinical monitoring for toxicity of ART

- The major causes of drug discontinuation in the first 3-6 months after initiating ART are due to drug toxicities; and hence, they must be closely monitored. They occur from few weeks to months.
- All patients require clinical evaluation at least every month in the first 6 months for ARV related toxicity. Subsequent follow-up can be done by months.
- The most frequent drug adverse reactions include:
  - ✓ Toxicities of NNRTIs (NVP and EFV) occurring in the first few weeks, and may be life- threatening.
  - ✓ ABC hypersensitivity reaction starting from first week following initiation.
  - ✓ Anemia and neutropenia due to AZT occur in the first 3 months.
  - ✓ Intolerance to certain drugs, in particular AZT induced gastrointestinal problems, are important barriers to adherence unless appropriate measures are taken.
- The clinical manifestations due to hypersensitivity reactions (ABC and NVP) may be confused with IRIS.
- **Laboratory monitoring for toxicity of ART:** look at IX section Above

5.4 Post-exposure prophylaxis (PEP) and Pre-exposure prophylaxis /PrEP/

Steps to manage potential HIV exposed person

1. **Treat the exposure site /immediate measures**
   - Percutaneous injury or injury to non-intact skin:
     - ✓ Wash exposed site with soap & water ASAP, without scrubbing
     - ✓ Avoid using antiseptics.
     - ✓ Allow free bleeding but do not squeeze the wound.
   - Exposed mucous membranes:
     - ✓ Irrigate copiously with clean water or saline.
2. **Report the exposure:** To PEP focal person or ART physician or nurse in the facility immediately to handle the case based on the national programmatic recommendations
3. **Start PEP;** PEP is a medical emergency - If possible, administer the first dose within 2 hours of exposure.

PEP recommendations based on risk assessment (Look at the table below)

- PEP is indicated for occupational exposures with a percutaneous, mucous membrane and non-intact skin exposure with potentially infectious body fluids.
- If the HIV status is unknown, starting empiric PEP and confirming the source patient HIV status is very critical to weight the benefit against the cost of treatment continuation.
- If the source patient is inaccessible for HIV testing for any reason, empiric PEP is recommended regardless of the knowledge of HIV status particularly for high-risk exposure settings or high-risk source patients. For instance, if the source is at high risk for HIV infection (eg, injection drug users) or has

symptoms suggesting HIV infection or risky exposure setting (e.g., needle stick from a sharps container in an HIV clinic).

Table: Recommended PEP based on risk assessment

Source HIV status	Recommendations to potential infectious body fluid occupational exposure*
Source patient is HIV **positive** (symptomatic or asymptomatic)	3 drug PEP (preferred regimen: *TDF +3TC+DTG*) **
Source patient HIV status is **unknown**	Give 3 drug PEP while awaiting HIV testing
Source patient is HIV **negative**	No PEP warranted

- **Extended PEP (3-Drug Regimen or Triple FDC):**
  - ✓ **TDF+ 3TC + DTG, Once daily for 28 days (Triple FDC;** TDF 300mg, 3TC 300mg, DTG 50mg**)**
    - Raltegravir (400 mg BID) or boosted PI based regimen may be used in pregnant mothers

    Or
  - ✓ **TDF + AZT + 3TC + LPV/r, PO, BID for 28 days** (AZT 300mg, 3TC 150mg, LPV/r 400mg/100mg)

    Or
  - ✓ **TDF + AZT + 3TC + ATV/r, PO, daily for 28 days** (ATV/r 300mg/100mg)

*Infectious body fluids include *blood, semen, vaginal secretions, any body fluids contaminated with visible blood, as well as cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids are potentially infectious. On the other hand, feces, nasal secretions, saliva, gastric secretions, sputum, sweat, tears, urine, and/or vomitus are not considered infectious unless they contain blood;*

**3 drug PEP preferred over two drug regimen and should be given within 72 hours for 28 days.

Timing and duration of initiation of prophylaxis:

- ☛ PEP is a medical emergency.
- ☛ To be effective, PEP should commence ASAP (within 1 - 2 hours). The maximum delay for initiation of treatment which would prevent infection is not known in humans.
- ☛ Do not consider PEP beyond 72 hours post exposure.
- ☛ Prophylaxis is to be given for 28 days.

Testing and monitoring after occupational exposure:

- **Testing source:**
  - ✓ If the source is negative no need for further assessment of the exposed victim is needed. If the source is positive, tasting the exposed person is needed.
- **HIV serology test of the exposed person**:
  - ✓ Immediately after exposure.
  - ✓ If the result is positive no need for PEP, but **if negative administer PEP ASAP** as outlined above and then **repeat serology at 6 weeks, 3 months, and 6 months.**
  - ✓ HBV Testing (screening) is also recommended.

- NB: initiate PEP immediately after exposure until test result confirms the HIV status of the victim. Stop PEP if the health worker is positive for HIV antibodies.
- Following HIV exposure there is a need for psychosocial support.

Prevention of Transmission of HIV after Sexual Assault

- Need counseling about potential risk of HIV infection
- Know the victim's HIV status prior to PEP
- Encourage patient to be tested ASAP with a delay not > 72 hours
- Inform possibility of transmitting infection during sero-conversion
- **Instruct to return at 6 weeks and 3 months post sexual assault for PICT.**
- Post-rape prophylaxis should be monitored & evaluated for:
  - ✓ **Emergency contraceptives**
  - ✓ Psychosocial and legal support
  - ✓ **Screening for conventional STIs and follow-up management**
  - ✓ Drug side effects
  - ✓ Sero-conversion
- **Recommended PEP for post sexual Assault HIV exposure**
  - ✓ AZT/TDF + 3TC + DTG for 28 days. Alternatively, Kaletra or boosted Atazanavir can substitute DTG

Follow-up of client exposed to HIV

- **Post exposure testing**
  - ✓ A client who is taking PEP should be followed in adult ART clinic
  - ✓ Instruct to return at 6 weeks, 3 months and 6 months post sexual assault for PICT.
- **Monitoring and management of PEP toxicity**
  - ✓ Reassessed within 3-5 days for medication tolerability and toxicity.
  - ✓ A further risk assessment re-evaluation may also be appropriate as necessary
  - ✓ Drug toxicity should be tested at baseline and again 2 weeks after starting PEP.
  - ✓ The scope of testing is based on medical conditions of candidate and toxicity of drugs included in PEP regimen.
  - ✓ Minimal, lab monitoring for toxicity includes CBC and LFT.
  - ✓ If toxicity is noted, modification of regimen should be considered.

Pre-Exposure prophylaxis (PrEP)

- Oral PrEP of HIV is the use of ARV drugs by people who are not infected with HIV but at a substantial risk.

- Substantial risk of HIV infection is defined as incidence of HIV higher than 3 per 100 person-years in the absence of PrEP.
    - ✓ HIV-positive sexual partner, recent bacterial STI, high number of sex partners, history of inconsistent or no condom use and commercial sex work; In high HIV prevalence area or network; HIV-positive injecting partner sharing injection equipment.
- PrEP is aimed to block the acquisition of HIV.
- **Eligibility for PrEP**
    - ✓ Negative HIV test result before prescribing PrEP
    - ✓ No signs/symptoms of acute HIV infection
    - ✓ Normal renal function; no contraindicated medications
    - ✓ Known hepatitis B virus infection and vaccination status
- **Prescriptions for PrEP and follow-up**
    - ✓ Daily, continuing, oral doses of TDF+3TC or FTC, ≤ 90-day supply
    - ✓ Follow-up visits at least every 3 months to provide the following:
        - HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment
        - At 3 months and every 6 months thereafter, assess renal function
        - Every 3-6 months, test for bacterial STIs

5.5 PMTCT and treatment of RVI exposed infant [11]

- PMTCT (Prevention of mother to child transmission) of HIV have four prongs
    - ✓ Prong 1: **Primary prevention** of HIV infection
    - ✓ Prong 2: **Prevention of unintended pregnancies** in HIV-positive women → emphasizes reducing the number of unplanned or unwanted pregnancies and effective family planning counseling service
    - ✓ Prong 3: **Prevention of HIV transmission from women living with HIV to their infants** → addresses care for HIV-positive women during pregnancy, labor and childbirth, and breastfeeding and care for their infants.
    - ✓ Prong 4: Provision of **treatment, care, and support to women living with HIV, and their infants, partner, and families** → including on-going, chronic care and treatment for HIV-positive pregnant/postpartum women and their HIV-exposed and HIV-positive children both during and beyond the PMTCT intervention period.
- All HIV positive pregnant, laboring and lactating mothers will be initiated on HAART for life (TDF, 3TC and DTG).
- HIV positive woman already on ART at time of pregnancy should continue and stay on the same regimen.

Post-partum and Neonatal care

- Continue initial ART for those who are initiated earlier.

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[11] Details of PMTCT are beyond the scope of this text book. Here is a highlight to have knowhow only. It is better to link mothers, to PMTCT clinic, special ANC follow up and labor management is mandatory.

- **Start ART for HIV positive mothers** who are breastfeeding even if it was not started before (currently recommended regimen **TDF + 3TC + DTG**)
- **For mothers who fulfill** Acceptable, Feasible, Affordable, Sustainable and Safe **(AFASS)** feeding, **formula feeding should be considered** after thorough discussion with the family.
- **For those who do not fulfill AFASS**, **breastfeeding must be exclusive for 6 months** and complementary feeding should start at 6th month. Breastfeeding should be continued until the first year of life but not more than two years.

RVI exposed infant

- Give **Nevirapine plus zidovudine syrup for the first 6 weeks** and **continue NVP syrup only for the next 6 weeks** for all HIV exposed infants (see table below for dosing).
- Zidovudine and nevirapine should be given during the first week of life. Start treatment ASAP after birth (within 48 hours)
- CPT should be started early
  - ✓ **Cotrimoxazole syrup (240mg/5ml), 48mg/kg/day, PO, BID**

Table; Enhanced Post-natal Prophylaxis (e-PNP) for HIV Exposed Infants

Infant age and duration of treatment	**Weight**	Dose
0-6 weeks	< 2500g	☛ Nevirapine syrup (50mg/5ml i.e.10mg/ml), 8 mg/kg/dose, PO, daily plus ☛ Zidovudine syrup (50mg/5ml), 2 mg/kg/dose, PO, BID
	> 2500g	☛ Nevirapine syrup (50mg/5ml), 12 mg/kg/dose, PO, daily plus ☛ Zidovudine syrup (50mg/5ml), 4 mg/kg/dose, PO, BID
6-12 week	Nevirapine syrup (50mg/5ml), 12 mg/kg/dose, PO, daily	

- **DNA/PCR should be done at 6 weeks of life** and HIV negatives should be followed as HIV Exposed Infant (HEIs).
  - ✓ DNA/PCR **positive** babies should be **linked to pediatric ART** for chronic HIV/AIDS follow up
  - ✓ Do **confirmatory rapid HIV antibodies test for DNA/PCR negative HEIs 6 weeks after the cessation of breastfeeding**
- Discharge negative babies for follow up after rapid HIV antibody test and link the positive babies to chronic pediatric HIV care, treatment and follow up.
- Give postpartum family planning counseling and provide mothers with family planning method of their choice as per the PMTCT guideline and post-partum care section of the protocol.
- Immunization and growth monitoring for the baby should be done the same way as non-HIV exposed babies
- The mother and infant should do their follow up at the MNCH clinic, where they can get integrated MNCH and HIV care.
- After discharge link the mother with ART clinic in the following scenarios:
  - ✓ If the baby is DNA/PCR positive

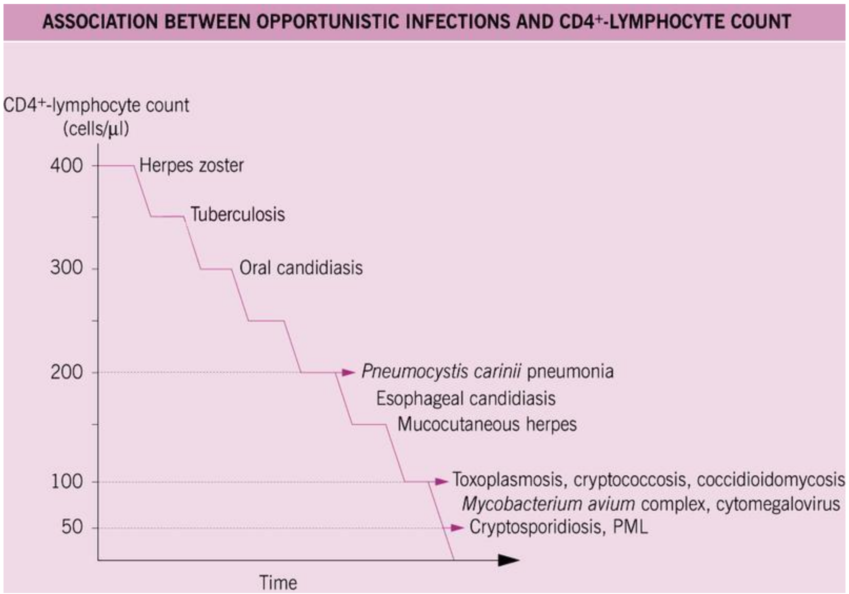
- ✓ If the baby is rapid HIV AB test positive
- ✓ If the baby is dead.
- ✓ If the mother develops any HIV/AIDS related complications of the disease or its treatment

Further reading

- MANAGEMENT PROTOCOL ON SELECTED OBSTETRICS TOPICS FOR HOSPITALS, December 2020, FMOH, Ethiopia
- WHO PMTCT guideline; ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS: TOWARDS UNIVERSAL ACCESS

5.6 Opportunistic infections (OI's)

- OIs are new or pre-existing conditions that occur when the immune system is impaired.
- They are the major cause of morbidity & mortality in HIV patients.
- Diseases directly caused by the HIV are not considered opportunistic diseases. E.g. HIV encephalopathy, HIVAN
- As the CD4 level declines, the risk of opportunistic infections increases. The level of immunity determines the occurrence and type of OIs.
- Most common OIs are both preventable & treatable.
- Screening and management of OIs is critical at any time of HIV care.
- Frequently affected organ systems are the **nervous, gastro-intestinal and respiratory systems, and the skin.**
- In general, milder infections such as herpes zoster and other skin infections occur early whereas serious life-threatening infections such as CNS toxoplasmosis and Cryptococcal meningitis occur later with severe immune-suppression.
- Some life-threatening infections, such as pneumonia and TB, may occur early as well as later. When TB occurs later it is atypical, more disseminated and more extra pulmonary


ASSOCIATION BETWEEN OPPORTUNISTIC INFECTIONS AND CD4+-LYMPHOCYTE COUNT

General strategies to prevent OIs are:

- Reduction of exposure
- Chemoprophylaxis (primary/secondary)
  - ✓ The 3 Chemoprophylaxis therapies practiced in Ethiopia;
    - CPT (cotrimoxazole preventive therapy)
    - IPT (INH preventive therapy)
    - Fluconazole
- Immunization and
- Starting HAART

Co-trimoxazole preventive therapy (CPT)

- An effective prophylaxis against:
  - ✓ Various bacterial infections: Streptococcus pneumoniae, Salmonella species, Shigella species, E. Coli, S. Aureus, H. Influenzae and Nocardia
  - ✓ PCP (Pneumocystis jirovecii)
  - ✓ Toxoplasmosis
  - ✓ Diarrhea caused by Isospora belli or Cyclospora
  - ✓ Malaria
- Dose; **cotrimoxazole 960 mg, PO, daily**
  - ✓ **for pediatrics; cotrimoxazole syrup (240mg/5ml), 48mg/kg/day, PO, daily.**

Table: CPT indication for primary prophylaxis

Age	Criteria for initiation	Criteria for discontinuation*	Monitoring approach
HIV exposed infants	In all, starting at 4 - 6 weeks after birth	Until risk of HIV transmission ends or HIV infection is excluded	clinical at 3-month Intervals
<5 years	In all	Discontinue for those older than 5 years of age who are clinically stable, with evidence of immune recovery (*CD4 cell count >350 cells/mm3*) and/or viral suppression on ART	
≥5 years, including adults	Any WHO stage and CD4 count ≤350 cells/mm3 Or WHO stage 3 or 4, irrespective of CD4 level	Discontinue in clinically stable patients (individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events) with: ✓ Evidence of immune recovery and/or viral suppression (CD4 count >350 cells/mm3, with viral load suppression) or ✓ Two consecutive CD4 count > 350 cells/mm3 if no viral load result	

- **Discontinue also if the person has SJS (Stevens-Johnson syndrome), severe liver disease, severe anemia, severe pancytopenia or negative HIV status.*
- ***Contraindications** to CPT: severe allergy to sulfa drugs; severe liver disease, severe renal disease*

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and G6PD deficiency.

Isoniazid Prophylaxis Therapy (IPT)

Look at under RVI TB below

Fluconazole prophylaxis

- Indication
  - ✓ After completing treatment for Cryptococcal meningitis
- Dose: 200mg Po daily

5.6.1 Respiratory system OI's

- Both URTIs & LRTIs are common
- Leading causes of death
  - ✓ Bacterial — **Strept. pneumonia**, H. influenza, legionaries, nocardia, *Rhodococcus equi, S.*aureus, G-ves (klebsella), **Mycobacteria** (TB, MAC)
  - ✓ Viruses — CMV, EBV
  - ✓ Fungal — **PCP,** Cryptococcus, histoplasmosis, candida, mucoromycosis
  - ✓ Protozoal — toxoplasmosis
  - ✓ Neoplastic — **Kaposi sarcoma, lymphoma**
  - ✓ Idiopathic — lymphoid and idiopathic interstitial pneumonia

5.6.1.1 RIV - TB coinfection

- TB is the most frequent life-threatening OI and a leading cause of death among HIV infected people.
- TB increases HIV replication through immune activation, thus high viral load and rapid progression of HIV disease.
- On the other hand, HIV increases susceptibility to M. tuberculosis infection (20-37 times greater lifetime risk than HIV negative), progression to TB disease and the incidence and prevalence of TB. This necessitates collaboration among the two programs.

Impact of HIV on TB

- Increases rate of TB re-activation, progression and active TB
- Increases TB morbidity and mortality (5 - 14-fold)
- Alters clinical manifestations of TB
- ☛ The clinical manifestations of TB in HIV-infected patients are influenced by the degree of immunosuppression.
- ☛ Early in the course of HIV disease, the clinical presentation of TB is similar to that of HIV-uninfected patients; symptoms include fever, cough, weight loss, fatigue, loss of appetite, night sweats, and hemoptysis.

- As immunity declines, the frequency of pulmonary cavitation and hemoptysis also declines.
- HIV-infected patients with advanced immunosuppression are at increased risk of extrapulmonary TB and disseminated TB. Virtually any site can be involved; the most common presentations are lymphadenitis and pleural involvement.
- Septicemic-like illness with hypotension can occur, with high mortality rate unless diagnosed and treated rapidly. In contrast, active tuberculosis may be subclinical in some patients with advanced immunosuppression, with no symptoms and a normal chest radiograph.
- Creates diagnostic challenges → **TB diagnosis in HIV infected patients is difficult**
  - Clinical manifestations become more **atypical** as immune function deteriorates
    - Sputum-smear negativity (up to 40% in culture proven pulmonary cases), atypical CXR finding, lack of classic granuloma formation in the late stages, and a negative TST
  - Negative AFB smear or Gene Xpert do not rule out PTB
  - Extra pulmonary manifestations are common than pulmonary TB
  - Empiric anti-TB may be warranted in many circumstance
  - Complicates treatment

Impact of TB on HIV

- TB infection activates T-cells, indirectly supporting HIV replication
- Accelerates HIV disease progression → Active TB is associated with increased HIV-1 viral load, progression to AIDS, high mortality

Table; Timing of ART for adults and children with TB

Patients with tuberculosis found to be HIV positive	**HIV positive patients taking ART diagnosed with TB**
➢ **Start ART in all TB patients**, including with drug-resistant TB, **irrespective of the CD4 count.** ➢ **Start anti-TB treatment first, followed by ART ASAP within the first 8 weeks.** ➢ It is recommended that ART be initiated as soon as TB therapy is tolerated. Ideally, this may be **as early as 2 weeks and not later than 8 weeks.** ➢ **If profound immune-suppression** (such as CD4 count < 50 cells/ mm^3), **ART** should be started immediately **within the first 2 weeks of initiating TB treatment.** ➢ Patients who present with TB before initiation of ART the preferred regimen are EFV containing first line regimen ➢ **TDF+3TC+ EFV** is preferred regimen for TB/HIV co-infected adult regardless of pregnancy status. ➢ **Efavirenz is a preferred drug** in patients starting ART while on	➢ Start anti-TB ➢ Modify ART regimen to avoid drug-drug interaction (e.g. change NVP with EFV) ➢ If patients develop TB while on ART for 3-6 months, continue ART throughout TB treatment and patients with NVP based treatment should be shifted to EFV. The recommended regimen is: TDF/3TC/ EFV or DTG ➢ Evaluate for treatment failure

Anti-TB treatment. When **second line** is initiated **LPV/r** is preferable.	

The 3 I's intervention for RVI - TB

A) **Intensify TB case finding and ensure quality TB treatment**
B) **IPT**
C) **Infection control**

I. Intensify TB case finding and ensure quality TB treatment

- All HIV positive clients should be informed about risk of developing active TB and the advantages of being screened for TB.
- Asses sign and symptoms of active TB (may have atypical presentation) and contact history with TB case
- If the evaluation shows no TB, children should be offered IPT, if no contraindications, regardless of their age.
- **Diagnosis of TB is challenging in HIV positive individuals**, especially when the stage of the disease is advanced.
- Thorough clinical evaluation, including exclusion of other OI, should be done. Acute bacterial pneumonia or PCP may occur in patients with underlying tuberculosis and patients should therefore be reevaluated for tuberculosis, particularly if respiratory symptoms persist after treatment.

Clinical manifestations:

- Variable, depending on CD4 count
- In early HIV - TB presents in a typical manner
- In late stages of HIV, when CD4 is <200, a primary TB - like pattern with **atypical clinical & CXR findings are common**
  - ✓ Extra-pulmonary and disseminated disease is more likely (70%)
  - ✓ Common extrapulmonary sites are: LNs, Pleura, Pericardium, CNS, GI, Kidney, Bone.
- **TB IRIS**: Paradoxical or Unmasking type

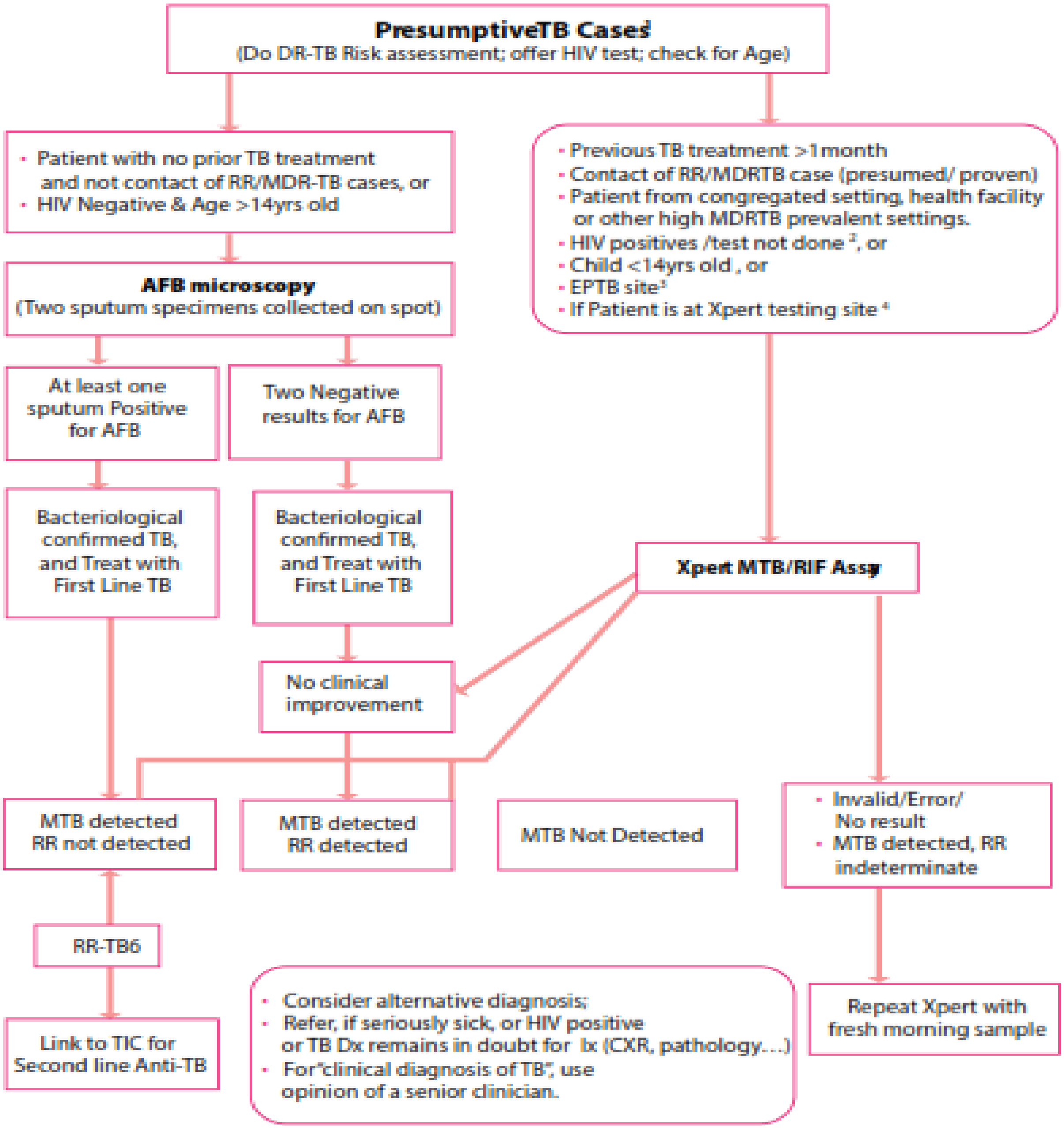
Diagnosis and IX

- **"TB suspect"** is defined by one or more of following:
  - ✓ Cough > 2 weeks
  - ✓ Constitutional symptoms (fever, weight loss, night sweats, contact history)
  - ✓ CXR suggestive of pulmonary TB
- **GeneXpert Test (XPert MTB/RIF Test) is the preferred initial diagnostic test**
  - ✓ Recommended as an initial diagnostic test for all presumptive TB cases (individuals wih TB symptoms) among HIV infected people.
  - ✓ One sputum sample for the facility which have Xpert test and two samples for sample referring facilities
  - ✓ Should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having HIV-associated TB or multidrug resistant TB.
  - ✓ It is also a preferred initial test for CSF specimens if TB meningitis suspected.

  - ✓ May be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extra pulmonary TB.
- ➢ **AFB microscopy (**2 spot tests with in 1 hour**):** if access to XPert MTB/RIF test is limited.
- ➢ **CXR**
  - ✓ **Early HIV**
    - **typical** adult TB features (with upper-lobe infiltrates/cavitation, no significant LAP or pleural effusion)
  - ✓ Late HIV → **Atypical** clinical & CXR findings are common
    - Lower/middle lobe opacity, little or no cavitation, interstitial / milliary pattern, adenopathy (hilar, paratracheal), Pleural/ Pericardial effusion
    - CXR MAY BE NORMAL
- ➢ **Sputum culture:** In patients with XPert negative results, sputum culture may be indicated. **Culture is the gold standard**

Diagnosis of extra-pulmonary tuberculosis in HIV positive

- ➢ Extra-pulmonary tuberculosis is more HIV-related than pulmonary TB.
- ➢ The accurate diagnosis of extra-pulmonary tuberculosis is complex and difficult, particularly with limited diagnostic capacity. Therefore, it is important to have high-index of suspicion and critically evaluate through clinical algorithms.
- ➢ If available, do organ specific investigations.


PresumptiveTB Cases[1]
(Do DR-TB Risk assessment; offer HIV test; check for Age)
Patient with no prior TB treatment and not contact of RR/MDR-TB cases, or
HIV Negative & Age >14yrs old
AFB microscopy
(Two sputum specimens collected on spot)
At least one sputum Positive for AFB
Two Negative results for AFB
Bacteriological confirmed TB, and Treat with First Line TB
Bacteriological confirmed TB, and Treat with First Line TB
No clinical improvement
Previous TB treatment >1month
Contact of RR/MDRTB case (presumed/ proven)
Patient from congregated setting, health facility or other high MDRTB prevalent settings.
HIV positives /test not done[2], or
Child <14yrs old, or
EPTB site[3]
If Patient is at Xpert testing site[4]
Xpert MTB/RIF Assay
MTB detected RR not detected
MTB detected RR detected
MTB Not Detected
Invalid/Error/ No result
MTB detected, RR indeterminate
RR-TB6
Link to TIC for Second line Anti-TB
Consider alternative diagnosis;
Refer, if seriously sick, or HIV positive or TB Dx remains in doubt for Ix (CXR, pathology…)
For"clinical diagnosis of TB", use opinion of a senior clinician.
Repeat Xpert with fresh morning sample

Algorism for Diagnosis of RVI - TB;

[1] Presumptive TB is defined as having symptom and signs consistent with TB; mainly persistent cough of two or more weeks (or cough of any duration if HIV positive).

[2] For patients in whom “HIV test is not done” at time of TB evaluation, Xpert test may be the initial test if the clinician has strong clinical suspicion of HIV infection or if the patient possesses risk behavior to acquire HIV infection.

[3] Liquid specimens from EPTB site (in particular CSF) may be subjected to Xpert test without additional processing.

[4] Xpert test is preferred test to examine presumptive TB patients identified at facility where the machine is available.

[5] Broad spectrum antimicrobials, excluding fluoroquinolone or anti-TB drugs is to be given for 10-14days.

[6] RR-TB result in patients considered to be low risk for MDR-TB warrants DR-TB risk re-assessment and a repeat Xpert test on fresh specimen, and if result

shows RR-TB again; link the patient to TIC for Second line TB treatment; but if the repeat test result identifies TB but not RR-TB, initiate first line TB regimen as bacteriologically confirmed susceptible TB at TB clinic.

☛ **Antibiotic trial:** has a role to treat concomitant bacterial infection for people living with HIV having cough or serious illness, but not helpful in the diagnosis of TB in HIV positives.

Table: Extra pulmonary TB diagnostic approaches in HIV positive patients

Type of TB	Evidences Strongly Suggestive of EPTB	Investigations and recommendations
Lymph Node TB	➢ ≥ 2cm in size ➢ Asymmetrical / localized ➢ Painless swelling ➢ Firm/ fluctuated ➢ Cervical location ➢ patient with weight loss, night sweats, fever	➢ LN Aspirate for AFB has 85% yield ➢ If not possible to do FNAC of LN, start anti-TB.
Pleural effusion	➢ Unilateral effusion ➢ Pleural fluid analysis shows; ✓ Clear and straw colored ✓ Clots on standing in a tube without anti- coagulants ✓ Protein >30g/L & >50% lymphocytes ➢ Patients with weight loss, night sweats, fever, or evidence of TB elsewhere	Start anti-TB ASAP.
Tuberculosis Meningitis	➢ Patients with weight loss, night sweats, fever ➢ CSF is clear with high protein, low glucose and lymphocytes ➢ Cryptococcal antigen (or Indian Ink and fungal culture) negative in CSF Evidence of TB elsewhere	➢ Admit patient, start anti-TB with steroids ASAP. ➢ Start treatment for cryptococcal meningitis based on clinical or lab evidences. ➢ **Note:** GeneXpert test has to be conducted on CSF specimen as an initial diagnostic test as much as possible.
Pericardial Effusion	➢ Hemodynamically significant pericardial effusion, often with pleural effusions, Lung fields clear and intra-thoracic lymphadenopathy. ➢ Usually patients with weight loss, night sweats, fever. ➢ **N.B.** 90% of Pericardial Effusions in HIV positive patients in high-TB burden areas is due to TB.	➢ CXR, Echo or chest ultrasound; pericardiocentesis, and pericardial biopsy; routine TB Workup. ➢ Start anti-TB ASAP
Disseminated TB	➢ Patients with weight loss, night sweats,	Start anti-TB treatment (add antibiotics if

	fever and cough ➢ Abnormal CXR (which can include miliary pattern) ➢ Large spleen/liver, Anemia	critically ill)
TB of the Spine	Pain over localized area, children/ adolescents - often thoracic vertebrae. Adults: frequently lumbar vertebrae.	➢ Spinal imaging (e.g. X-Ray, MRI) ➢ FNA of vertebral lesions and/or paraspinous abscesses when feasible.

II. TB prevention with IPT (isoniazid preventive therapy)

- IPT is the use of Isoniazid to sterilize (prevent reactivation) latent TB infection.
- **Screening for exclusion of active TB in HIV infected persons is the single most important step** that should precede the decision to initiate IPT.
- The dose of **INH is 300mg/day for adults and 10mg/kg for children for 6 months.**
- It is also desirable to provide **pyridoxine** (**vitamin B6), 25mg/day, to prevent INH-induced peripheral neuropathy.**

Contraindications of IPT;

- Individuals with any one or more of the following conditions should not receive IPT:
  - ✓ **Symptoms** compatible with **tuberculosis** even if the diagnosis isn't yet confirmed.
  - ✓ **Active hepatitis** (chronic or acute)
  - ✓ Regular and heavy **alcohol** consumptions
  - ✓ Prior **allergy or intolerance to isoniazid**
  - ✓ Symptoms of **peripheral neuropathy**

NB: Past history of TB and current pregnancy should not be contraindications for starting IPT.

National policy:

- IPT should be administered at enrolment to HIV care after ruling out active TB.
- IPT is to be administered once and should not be repeated unless there is strong indication on its benefits which is to be **decided by senior physician**.
- IPT should be **administered only for 6 months.**
- IPT should not be administered right after completing full course of TB treatment
- IPT can be administered for patients who had history of TB treatment before 3 years.

Follow-up of patients on IPT

- Patients should be given monthly supply of Isoniazid for the first 3 months and 3 months' supply for the remaining months.
- At each follow-up visit assess;
    - ✓ Adherence to treatment and educate client
    - ✓ Drug toxicity.
    - ✓ Signs and symptoms of active tuberculosis or other OI.
    - ✓ Stop IPT if active TB is diagnosed and to immediately start anti-TB.

Treatment interruption management

- IPT is said to be completed if a patient completed the full course of therapy within 9 months period (i.e. the six months doses should be finished in nine months' time).
- If the client discontinues treatment for a period of **< 3 months: Resume the same course by adding for the missed doses at the end**.
- If the client discontinues treatment for a period of **> 3 months: Re-initiate new course of IPT for 6 months.**

Repetition and prolongation of IPT:

- **Repeating IPT** after the first cycle of IPT or the provision of IPT after completion of full course of TB therapy **is not recommended in Ethiopia**.

Provide HIV testing and counseling to presumptive and confirmed TB patients

- Among TB-HIV co-infected patients, other OIs are significant causes of morbidity and mortality even with a successful treatment of TB, necessitating routine HIV testing and counseling to all TB patients.

Presumptive treatment of TB for people living with HIV

- To prevent the death of people with HIV in situations where expedited diagnosis of TB is not possible or feasible due to the clinical condition of the patient or limited access to TB diagnostic services.
- No case definition for presumptive TB.
- WHO algorithms include initiation of TB treatment for people with HIV in peripheral facilities based exclusively on clinical suspicion (without TB investigations) for seriously sick patients (with respiratory distress) based on the judgment of the clinician.
- However, every effort should be made to confirm the diagnosis of TB after initiation of presumptive treatment and that treatment should be stopped only if there is bacteriological, histological or strong clinical evidence of an alternative diagnosis.

Introduce HIV prevention interventions for presumptive and confirmed TB patients

- All clients attending TB clinics should be screened for STI using a set of simple questions.
- Those with symptoms of STI should be treated or referred to the treatment providers.
- Condoms should be made available in TB clinics.

Infection control

- People living with HIV are at high risk of acquiring TB in health care facilities and congregate settings.
- Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental and personal protection measures to reduce the transmission of TB in health care and congregate settings and surveillance of TB disease among workers.

Summary of recommendations for key actions of infection control

- Taking Administrative, Health worker and care provider, Environmental and personal level protective measures
- Provide HIV testing and counseling to presumptive and confirmed TB patient
- Presumptive treatment of TB for people living with HIV
- Introduce HIV and other STI prevention interventions for presumptive and confirmed TB patients
- Provide CPT for HIV positive TB patients
- Ensure HIV prevention, treatment and care for HIV positive TB patients

MDR (Multidrug-resistant) TB and HIV

- Xpert MTB/RIF is the preferred test where possible, since this it is more sensitive for detecting TB among people with HIV and rapidly detects rifampicin resistance, thus greatly shortening the time to diagnose and treat MDR-TB.
- The burden of MDR-TB can be reduced by strengthening HIV prevention, improving infection control and collaboration between HIV and TB control activities, with special attention to the groups at the highest risk of MDR-TB and HIV infection, such as people who inject drugs and those exposed in congregate settings.

5.6.1.2 Pneumonia in RVI patient

1. Bacterial pneumonia

- Bacterial pneumonia tends to be more severe and recurrent as the CD4 counts drops significantly.
- Pneumonia can also concomitantly present with sinusitis and/or bacteremia.
- If not treated promptly, extra pulmonary complications like empyema, meningitis, pericarditis, hepatitis and arthritis can follow.
- Management is the same as non-RVI patients (for more click here → Pneumonia (የሳንባ ምች))

2. Pneumocystis pneumonia (PCP)

- Caused by Pneumocystis jiroveci, formerly known as pneumocystis carini pneumonia, classified as a fungus but also have characteristics of protozoa.

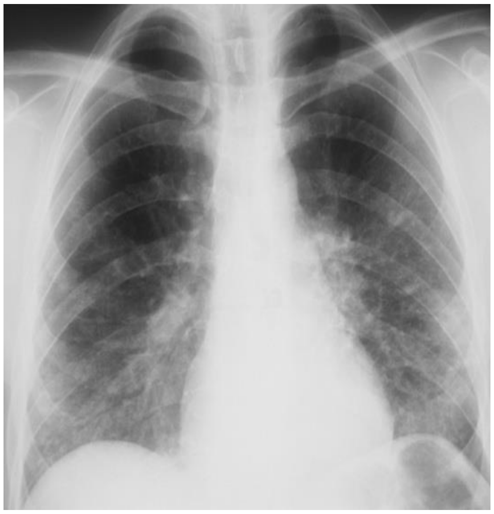
- It frequently causes pneumonia among immuno-compromised individuals.
- It commonly occurs when patients have significant immune suppression (CD4 < 200cells/mm3 or CD4 percentage < 14%).

Clinical manifestation

- Typical have an insidious (sub-acute onset over 2 to 4 weeks) onset of low-grade fever, dry cough, fatigue and progressive dyspnea exacerbated by exertion.
- Patients will have an increasing tachypnea, tachycardia and cyanosis as the disease progresses.
- Physical examination reveals fever, tachypnea, tachycardia and scattered rales in the lungs but examination of the lungs can appear normal in some patients.
- In children highest incidence is seen between 2-6 months of age and is characterized by abrupt onset of fever, tachypnea, dyspnea and cyanosis.
- Due to non-specific presentation, PCP should always be considered in those patients with evidence of moderate to severe immunosuppression who come up with cough, progressive dyspnea or fatigue.

Investigations and diagnosis

- **Clinical Dx;** presumptive diagnosis of PCP is based on clinical judgment
- **Chest X-ray: a perihilar interstitial infiltration with tendency to spread outwards is Typical finding**. Can be **normal in 20%** of patients.



Picture; Bilateral interstitial infiltrates beginning in the perihilar regions (ground glass appearance)

- **Culture**: **definitive diagnosis of PCP**. Induced sputum sample using special stains like Giemsa or methylamine silver stains, but these tests are not routinely done in Ethiopia.

Treatment

- Oxygen should be given in moderate and severe cases.

First line:

- **Cotrimoxazole, 960mg (15-20mg/kg/day), P.O/IV, TID/QID for 3 weeks**
    - ✓ Give the same medicine IV if the patient is not able to swallow the medicine and shift orally when tolerable.
    - ✓ Close monitoring is necessary during the initial 5 days of treatment and if patient grows sicker, administration of oxygen is useful.
    - ✓ **In severely ill patients** with marked respiratory distress and extensive chest X-ray findings **prednisolone has to be given simultaneously**
    - ✓ Toxicity of co-trimoxazole, like skin rash, bone marrow suppression, hepatitis and renal failure can be troublesome in some patients with advanced HIV disease and requires close monitoring. SJS (Steven Johnson syndrome) may occur if the patient is allowed to take the medicine after the development of rash.
    - ✓ Secondary prophylaxis after completion of the course of treatment with **CPT** should be continued.

Alternative:

- **Clindamycin+ Primaquine or Dapsone** for 3 weeks
    - ✓ **Clindamycin**, 600 mg BID (300-450mg P.O., TID) for 3 weeks PLUS
    - ✓ **Primaquine**, 30mg base P.O, daily (15 mg BID) for 3 weeks.

      OR
    - ✓ **Clindamycin** 600 mg QID, for 3 weeks plus
    - ✓ **Dapsone** 100 mg daily for 3 weeks.

      OR
    - ✓ **Trimethoprim,** 20mg/kg/day, P.O, QID for 3 weeks PLUS
    - ✓ **Dapsone,** 100mg P.O., daily for 3 weeks

      OR
    - ✓ **Pentamidine** Isethionate, 4mg/kg I.V. daily for 3 weeks. It should be given to those who fail to tolerate the above regimen.

N.B.

- ☛ Typically, a mild rash with fever develops 7 to 10 days after initiation of therapy.
- ☛ Bone marrow suppression may occur, and CBC monitoring is useful.
- ☛ Possible hepatotoxicity and nephrotoxicity may also be evaluated at the 3rd week of therapy.
- ☛ Consider spontaneous pneumothorax in patients with sudden deterioration in clinical condition.

Adjuvant treatment

- **Corticosteroids → Indicated if SPO_2 <90%,** In the absence of pulse oximetry, clinical judgment should be used to select moderately to severely sick patients who benefit from corticosteroids.
    - ✓ **Prednisolone 40mg BID (i.e. 80 mg) for 5 days, then 20mg BID for 5 days, then 20mg daily until completion** of intensive co-trimoxazole therapy **(for 11 days).** No tapering from the 20 mg dose is necessary.

- ✓ **For severe PCP in children**: prednisolone 2mg/kg per day for the first 7 - 10 days followed by a tapering regimen for the next 10 - 14 days.

Pregnancy considerations

- The management and the prophylaxis for pregnant is similar to non-pregnant mothers.
- **TMP-SMX is the preferred drug in pregnant. However**, be aware of the theoretical risk of **teratogenicity in the first trimester** with the use of TMP-SMX.
- Aerosolized **pentamidine or oral atovaquone** can be used as **alternative** than discontinuing chemoprophylaxis in the first trimester

3. Lymphoid interstitial pneumonitis (LIP)

- One of the most common chronic lower respiratory conditions occurring in up to 25% of children with HIV/AIDS

Clinical manifestations

- Ranges from asymptomatic disease with isolated radiographic findings to bullous lung disease with pulmonary insufficiency.
- Symptomatic children present with insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales or wheezing.
- Progressive disease is accompanied by digital clubbing and symptomatic hypoxemia.
- Associated physical findings include generalized, hepatosplenomegaly and parotid enlargement.

Diagnosis

- Usually based on clinical examination findings, diffuse bilateral reticulonodular infiltrate on X-ray with mediastinal lymphadenopathy.
- It is important to exclude tuberculosis and other infectious etiology.

Treatment

- Symptomatic treatment (hydration, oxygen).
- Antibiotics: if there is a superimposed bacterial infection.
- Bronchodilators: may be helpful in mild to moderate disease.
- Corticosteroids: reserved for children with significant hypoxemia and symptoms of pulmonary insufficiency. Give prednisolone 1- 2 mg/kg/day for 6 - 8 weeks and then taper as tolerated.

5.6.2 Gastrointestinal (GI) opportunistic diseases

- GI OIs commonly manifest with diarrhea, nausea and vomiting, dysphagia and odynophagia among others.

- Most common causes among HIV infected are Isospora belli, cryptosporidium, shigella and salmonella, CMV etc.
- A scenario of multiple concurrent GI infections is fairly common.
- A number of drugs with similar effects can pose challenges in differential diagnosis.
- **Infectious** OI
  - ✓ Candida
  - ✓ Bacterial
  - ✓ HSV
  - ✓ EBV
  - ✓ CMV
- **Non- Infectious**
  - ✓ Angular chelitis
  - ✓ Malignancies (kaposi's sarcoma/KS/, lymphoma)
  - ✓ Aphthous ulcers
- Oral — candidiasis, aphthus ulcer, kaposi's sarcoma, gingivitis, periodontitis, oral hairy leukoplakia
- Esophagus — esophagitis due to candida, CMV, HSV, KS

The general **principle of managing** GI OIs

- ✓ Identifying and treating the specific offending agent and
- ✓ Providing supportive care to monitor situations such as fluid loss.

5.6.2.1 Candida infection

Dysphagia and odynophagia

- Dysphagia (difficulty in swallowing) and odynophagia (painful swallowing) are symptoms of esophagitis occurring at advanced stages of AIDS.
- They are usually caused by candida, HSV, CMV, and aphthous ulcers.
- As well as a sign of severe immunodeficiency, esophagitis also seriously impairs the patient's nutritional status. Therefore, prompt diagnosis and treatment are mandatory to avert nutritional complications and inability to swallow prescribed medications.
- Children will present with reluctance to eat, excessive salivation, or crying while feeding.
- If thrush is associated with dysphagia, odynophagia, and/or retrosternal pain, consider esophageal candidiasis but this can also occur in the absence of oral thrush.

Table: *Candida* Infection management

	First line	Alternative	Duration
Oropharyngeal candidiasis	➢ Fluconazole 100-200 mg PO, daily (3mg/k/day in children) or	➢ Posaconazole 400 mg PO BID on day 1, then daily or ➢ Miconazole buccal tablets 50 mg PO daily or	7 - 14 days

(oral trush may occur in > 90% of HIV/AIDS patients in any time)	➢ Itraconazole 200 mg PO daily or ➢ ketoconazole 200 mg BID (3-6mg/kg/day daily in children)	➢ Clotrimazole troches 10 mg PO five times daily or ➢ Nystatin 5 mL (100,000 units/mL)- swish and swallow 4 or 5 times daily	
Esophageal candidiasis (majorly an extension of oral trash but not always)	➢ Fluconazole 100 - 400 mg PO/IV daily or ➢ Itraconazole 200 mg PO daily	➢ Posaconazole 400 mg PO BID on day 1, then daily or ➢ Other azoles or ➢ Caspofungins or ➢ amphotericin B	14 - 21 days
Vulvovaginal candidiasis	➢ Fluconazole 150 mg PO, stat or ➢ topical azoles (e.g. miconazole vaginal pessary) for 3 - 7 days	➢ Itraconazole 200 mg orally daily for 3 - 7 days ➢ Boric acid 600 mg vaginal suppository once daily for 14 days for azole refractory candidiasis ➢ Severe or recurrent vaginitis: oral fluconazole (100—200 mg) or topical antifungals for ≥7 days	3 - 7 days

- Risk of recurrence after completing treatment may be high.
- If the patient is on ART, s/he should be investigated for treatment failure.
- Take necessary precautions regarding drug interactions especially with ketoconazole.
- Patients may need hospital admission for supportive care till the oesophageal symptoms improve and necessary long-term treatments are started.
- **If diagnosis suggests HSV esophagitis use acyclovir 400mg po 5 times daily for 14 to 21 days.**

Prevention

- Administration of ART and immune restoration is an effective means to prevent disease.
- ART failure should be investigated if there is recurrent infection.
- Routine primary prophylaxis is not recommended.
- Secondary prophylaxis or chronic suppressive therapy is not also recommended unless frequent or sever recurrence, if used (Fluconazole 100 mg PO once daily for oral/esophageal and 150 weekly for VVC), discontinue therapy if CD4 count >200 cells/mm3.

Pregnancy

- Pregnancy upsurges the risk of vaginal colonization with Candida species.
- **Topical therapy is preferable** for treatment of oral candidiasis in pregnancy, but is essential for vulvovaginal candidiasis, especially during the first trimester.

- Chemoprophylaxis using **systemically absorbed azoles** against oropharyngeal, esophageal, or vaginal candidiasis **should not be initiated** during pregnancy or should be discontinued in women who become pregnant.

5.6.2.2 Aphthous stomatitis/ aphthous ulcer

- Unknown etiology
- Usually **painful & self-limiting**
- May interfere with swallowing.
- *Look at image under physical examination (patient approach in RVI) section of this chapter.*
- Rx:
  - ✓ General measures
    - **Oral hygiene**
    - **Avoidance of exacerbating factors** — Where possible, reduce traumatic factors inside the mouth (eg, sharp/rough dental restorations, braces). Avoid habits that cause trauma (eg, biting cheeks or lips) and foods that seem to exacerbate the process (Avoid spicy foods).
    - **Pain control** — Topical anesthetics provide immediate symptomatic relief of short duration;
      - ○ **2% lidocaine,** may be applied directly to surface of ulcers or used as a swish and spit
      - ○ **Diphenhydramine** liquid: 12.5 mg/5 mL; 5 mL swish and spit
      - ○ **Aluminum hydroxide, magnesium hydroxide, and simethicone** suspension: 5 to 10 mL swish and spit
    - **Control of secondary infection; Nystatin suspension** (400,000 to 600,000 units) swish and swallow four times daily or **Clotrimazole troches** (10 mg) four to five times daily
  - ✓ Topical steroids (Triamcinolone oral paste)
    - **Triamcinolone oral paste;** Press a small amount (about $^{1}/_{4}$ inch) to the lesion at bedtime; a larger quantity may be required for coverage of some lesions. For severe lesions, may be used 2 or 3 times daily after meals.
  - ✓ A short course of **oral corticosteroids** may be beneficial in patients with severe Recurrent aphthous stomatitis that is not controlled with topical therapies
    - **Prednisone,** 20 to 40 mg, PO, daily for 4-7 days.

5.6.2.3 Necrotizing Gingivitis

- Inflammation of the gums
- Extensive and necrotic
- Tooth loss
- **Anaerobic infection**
- Treatment
  - ✓ Amoxycillin 500mg PO TID for 10 to 14 days Plus
  - ✓ Metronidazole 500mg PO TID for 10 to 14 days
  - ✓ **Debridement** for severe cases

5.6.2.4 Herpes simplex (HSV1)

- Shallow, **clustered ulcers** around oral and peri oral area are characteristic
- May be solitary and deep in the severely immunocompromised patient
- Usually **painful**
- DDx: aphthous ulcers
- ***NOTE: Vesicles are rarely seen in the mouth!***
- Rx:
  - ✓ Local antiseptics to avoid superinfection
  - ✓ Acyclovir, 400 mg, PO, TID, for 1 week

5.6.2.5 Diarrhea *in HIV patients*

- Diarrhea is defined, as passing of > 3 loose or watery stools per day.
- It may be acute or chronic, persistent or intermittent.
- Diarrhea is among the most frequent symptoms of HIV disease.
- Delay in treatment can result in fluid loss and hemodynamic instability. Chronic diarrhea may also lead to nutritional deficiencies and wasting.
- Risk of a bacterial enteric infections (including bacteremia risk) increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/mm3.

Causes of Diarrhoea in HIV patients

- **Protozoal infection**:
  - ✓ *Cryptosporidium* species, *Isospora belli,* M*icrosporidium* species, *Entamoeba histolytica, G. lamblia,*
- **Bacterial infection**:
  - ✓ *Campylobacter*, *Shigella*, and *Salmonella* species
- **Toxin induced**:
  - ✓ *E. Coli* and *Clostridium difficile*
- **Mycobacterial infection**:
  - ✓ *M. avium* complex, *M. TB*
- **Helminthic infection**:
  - ✓ ***Strongyloides stercoralis***
- **Viral infection**:
  - ✓ CMV, HSV
- **Fungal infection**:
  - ✓ Histoplasmosis, coccidioidomycosis, and penicilliosis, *Candida* species (seldom a cause of diarrhoea)
- **Non-infectious disorders**:
  - ✓ Kaposi's sarcoma, lymphoma
- **AIDS enteropathy**:
  - ✓ Direct cytopathic effect of HIV disease
- **Drug Side effects**:
  - ✓ Antibiotics, ART

Laboratory evaluation

- **Stool microscopy** for ova or parasite, inflammatory cells **at least 3 times**
- **Modified AFB** staining for cryptosporidium, isospora belli
- **Stool culture when indicated** (optional).

Management

- Fluid and electrolyte replacement, nutritional support → The most important first step is correction of fluid loss. Depending on the severity of dehydration, **ORS or IV fluid therapy can be given**. Patients with severe dehydration need to be admitted for IV fluid administration.
- In children zinc 20mg per day for 10-14 days (10mg per day for infants < 6months of age) should be added
- If specific enteric pathogen is identified or strongly suspected on clinical grounds, it should be treated accordingly

Empiric treatment of bacterial enteric infections

- Pending Diagnostic Studies: For patients with advanced HIV (CD4 count <200 cells/mm3 or concomitant AIDS-defining illnesses) and clinically severe diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills); and/or patients with bloody diarrhea but repeatedly negative stool results especially with constitutional symptoms such as fever.

First line

- ✓ Ciprofloxacin 500—750 mg PO (or 400 mg IV), BID

Alternative

- ✓ Ceftriaxone,1 g, IV, daily or
- ✓ Cefotaxime, 1 g, IV, TID.

NB: Diagnostic fecal specimens should be obtained prior to empiric antimicrobial therapy initiation; and antibiotic susceptibilities should be performed in settings where microbiologic facilities are available to confirm and inform antibiotic choice given increased reports of antibiotic resistance.

- The **treatment duration** depends on the expected pathogen and may generally extend from **7—14 days for uncomplicated** cases and **2 to 3 weeks for complicated** (bacteremia, recurrent infection and/or advanced AIDS)
- Hospitalize and use IV antibiotic therapy if marked nauseas, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when there is a clinical judgment for severity of disease
- For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed.
- Prophylactic antimicrobial to prevent bacterial enteric illness is not usually recommended, including for travelers.

Table: Treatment of specific enteric pathogens

Agent	**CD4**	**Symptom**	**Diagnosis**	**Rx**
E. hystolytica	Any	Bloody stool,	Stool	Metronidazole

		colitis	microscopy	
Giardia		Watery diarrhoea		
Cryptosporidium	<150		Modified AFB	ART*
Isospora belli	<100			TMP-SMX
Microsporidium	< 50		Giemsa stain	Albendazole
CMV	<50	Watery/bloody diarrhoea, colitis	Tissue biopsy	Ganciclovir
**No specific treatment for Cryptosporidium but it will improve with immune restoration following ART.*				

Symptomatic treatment

- In adults use anti-diarrhoeal agents **Loperamide 4mg stat then 2mg after each bowel motion or Diphenoxylate 5mg QID**.
- Necessary caution should be taken to **avoid anti- diarrhoeal agents** in bacterial or parasitic **infectious colitis or enteritis**, **since toxic mega colon** may occur.
- Patients with chronic diarrhoea will develop nutritional deficiencies of variable severity; therefore, proper nutritional assessment and support are helpful.

Persistent Diarrhoea Management

- Empiric antibiotic Rx if 3 stool tests are negative and no blood in stool
  - ✓ **Cotrimoxazole or ciprofloxacin + metronidazole**
  - ✓ Consider albendazole for 2 wks
  - ✓ Treatment of lymphoma, Tb, MAC, ….
- If no response consider ART to boost immunity (for HIV enteropathy and non treatable OIs like Cryptosporidium)

5.6.2.6 Peri-anal problems

- A number of chronic or acute peri-anal problems commonly occur among Patient's living with HIV disease, particularly in advanced immunodeficiency. These include **recurrent peri-anal abscesses, chronic peri-anal fistula, peri-anal herpes** (severe, persistent and extensive), and **peri-anal warts** (sometimes large with obstructive problems).
- Patients with peri-anal problems frequently go to local healers and come with complicated situations.

Treatment of peri-anal abscess in adolescents and adults

- Can be easily diagnosed with DRE
- Early treatment is mandatory to avoid extension to peri-anal abscess depending on immunological status of patient and thus more serious morbidity.
- If **surgical incision** is required, it should be done promptly on first visit. Otherwise, **broad spectrum antibiotics** such as **Augmentin** or alternatively

amoxicillin or **ampicillin** must be administered in sufficient dose **for at least 10 days**.

- Palliative care including **Sithz baths and analgesics** are also important.

Peri-anal and/or genital herpes

- Latent or active infection with HSV I and II are common in the general population, and is usually mild in immune-competent persons.
- Severe cutaneous disease or visceral involvement is usually restricted to patients with advanced immunosuppression with a CD4 count <100 cell/mm3.
- The lesions become extensive, persistent, severe and sometimes with bleeding.
- Unless thorough evaluation with regular inspection of genital and peri-anal areas is done, patients very often don't complain about genital lesions.
- The response to **Acyclovir** is gratifying if it is done in sufficient dose (**400mg 4-5 time/day**) and sufficient duration (**10 days to 2 weeks** in moderately severe or severe cases).
- There is risk of **recurrence** with severe immunodeficiency. In such cases repeat treatment and put patient on chronic HIV care including ART.
- Herpetic oro-labial infection is treated the same way as ano-genital herpes
- The treatment of **anal and genital warts** is particularly frustrating when they are large.
- Unlike other OIs, the response to ART is not satisfactory.
- Patients who have very well responded immunologically with ART continue to suffer from the warts.
- Depending on the size, **cauterization, podophyllin** treatment and **surgical debulking**, etc. may be tried.

5.6.3 CNS opportunistic diseases

- Neurological manifestations of HIV can occur at any time from viral acquisition to the late stages of AIDS.
- They are varied and may affect any part of the nervous system including the brain, spinal cord, ANS and the peripheral nerves.
- HIV affects the nervous system in 70-80% of infected patients.
- The effect may be due to direct effect of the virus, OIs and/or malignancies.
- For certain neurological manifestations, a single aetiology is responsible while in others it is due to multiple causes.
- Most life-threatening neurological complications of HIV occur during the severe immunodeficiency state and specific aetiological diagnosis in the Ethiopian setting is often a major challenge.
- Diagnosis of neurological disorders in HIV in our setting depends on the history and standard neurological examinations.

Neurological complications in HIV patients may be due to:

- HIV (HIV encephalopathy)
- OIs (toxoplasmosis, crypotococcal meningitis)
- Neurosyphilis
- Malignancies (primary CNS lymphoma); and
- Drugs (e.g. EFV, etc.)

- Early in the course of HIV
  - ✓ Aseptic meningitis
  - ✓ GBS, CIDP
  - ✓ Transvers myelitis
  - ✓ Peripheral neuropathy
- Late stage HIV
  - ✓ Diffuse processes (meningitis, meningoencephalitis)
    - Cryptococcal, Tb, syphilitic, listeria, lymphomatous, aseptic (HIV 1) meningitis
    - AIDS dementia complex
  - ✓ Metabolic encephalopathies

Focal Neurological Deficit in HIV infected people

- ✓ Toxoplasmosis
- ✓ Tuberculoma
- ✓ Brain abscess
- ✓ Progressive Multifocal Leukoencephalopathy (PML)
- ✓ Syphilis
- ✓ Cryptococcoma
- ✓ Primary CNS Lymphoma
- ✓ Stroke/ vasculitis
- ✓ Viral encephalitis (HSV, VZ)

5.6.3.1 CNS Toxoplasmosis

- Toxoplasmic encephalitis (TE) is caused by the protozoan Toxoplasma gondii
- Disease appears to occur almost exclusively because of reactivation of latent tissue cysts in individuals with underlying immunodeficiency.
- Primary infection occasionally is associated with acute cerebral or disseminated disease.
- Sero-prevalence varies substantially in different communities; in Ethiopia, general prevalence is about 80%.

Clinical Manifestations

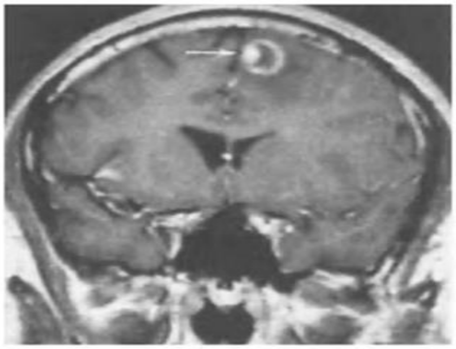
- **Focal encephalitis** with headache, confusion, fever and/or signs of FND (motor weakness) → **The most common clinical presentation** of T. gondii infection among patients with AIDS
  - ✓ Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, and coma.

- may also present with non-specific headache and psychiatric symptoms.

Investigations and diagnosis

- **Serologic test**
  - **IgG antibodies** → almost uniformly seropositive
  - **The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible.**
  - On the other hand, positive test or high titer for Ig-M would suggest a more recent infection. IgM antibodies usually are absent.
  - Quantitative antibody titers are not useful for diagnosis.

- **Neuro-imaging (CT scan or MRI of the brain)**
  - **Definitive diagnosis of CNS toxoplasmosis** requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample.
  - In the absence of imaging support, empirical treatment is justified when patients present with FND and the CD4 count is < 200 cells µl.
  - Failure to respond to conventional therapy, based on presumptive clinical diagnosis within a week or two of initiation of therapy, suggests the diagnosis to be unlikely.
  - With empirical treatment for toxoplasmosis, nearly 90% of patients will demonstrate clinical improvement within days of starting therapy.
  - Radiological evidence of improvement is usual after 14 days of treatment.



Figure; CNS toxoplasmosis. A coronal postcontrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (*arrow); this is so-called "**eccentric target** **sign"*** which is typical of toxoplasmosis.

Treatment

First line regimen in the Ethiopian context is:

- Cotrimoxazole (Trimethoprim/sulfamethoxazole) 80/400, 4 tablets, PO, BID, for 28 days, followed by 2 tablets BID for 3 months.

  - In children 10mg of trimethoprim + 50mg of sulfamethoxazole/kg/dose, BID for 28 days followed by maintenance therapy at 50% reduced dosage for 3 months.
- ✓ Maintenance treatment (Secondary prophylaxis): use co-trimoxazole 960mg daily for adults' and in children.

Alternative regimen

I.

- ✓ **Sulfadiazine**, 1-2 gm PO QID for 6 weeks or 3 weeks after resolution of lesion PLUS
- ✓ **Pyrimethamine**: loading dose of 200 mg stat, followed by 50-75 mg/day for 6 weeks. PLUS
- ✓ **Folinic acid (Leucovorin):** 10-20 mg/d for six weeks

OR

II.

- ✓ **Pyrimethamine and Folinic Acid** (Leucovorin): (standard dose) PLUS
- ✓ **Clindamycin:** initially 200-400mg I.V. then 600 mg QID (300-900mg)

OR

III.

- ✓ **Sulfadoxin Pyrimethamine**, 1000mg/50mg, P.O., BID for 2 days, and then one tablet/day for 6 weeks. PLUS
- ✓ **Folinic Acid (Leucovorin):** (standard dose) for 6 weeks
- ✓ Followed by Maintenance treatment with Pyrimethamine, 25mg/day PO, daily

Chronic maintenance treatment (Secondary prophylaxis) for TE:

- ➢ Co-trimoxazole 960mg daily for adults.
- ➢ Discontinuing chronic maintenance therapy if: successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 count >200 cells/mm3 for >6 months in response to ART.
- ➢ Reinitiate prophylaxis if CD4 count <200 cells/mm3

Other supportive measures

- ➢ Adjunctive **corticosteroids** should be used for patients with radiographic evidence of **midline shift**, **signs of critically elevated ICP** and **altered sensorium** or **clinical deterioration within the first 48 hours of therapy.**
  - ✓ **Dexamethasone** 4 mg (0.15mg/kg/dose for children) QID is usually chosen and is generally tapered over several days and discontinued ASAP.
- ➢ Anticonvulsants should be administered to patients with a history of seizures, but should not be given routinely for prophylaxis to all patients with the presumed diagnosis of TE. Careful attention needs to be paid to any potential drug interactions.

Primary prophylaxis

- ✓ Cotrimoxazole, 960mg PO, daily
- ✓ Indications for Initiating Primary Prophylaxis:
  - Toxoplasma IgG positive patients with CD4 count <100 cells/mm3

- ✓ When to discontinuing primary prophylaxis:
  - CD4 count >200 cells/mm3 for >3 months in response to ART
- ✓ Indication for restarting primary prophylaxis:
  - CD4 count <100 to 200 cells/mm3 (AIII)

Pregnancy considerations

- ➢ **Pyrimethamine and sulfadiazine** are considered safe in pregnancy.
- ➢ **Pyrimethamine** should **better be avoided during the first trimester** and **sulfa drugs** (including Sulphamethoxazole, sulfadiazine) have a potential risk of **neonatal kernicterus** upon exposures in late pregnancy though no clearly convincing data yet.
- ➢ The use of TMP (TMP-SMX) in the first trimester should also be evaluated against the potential risk

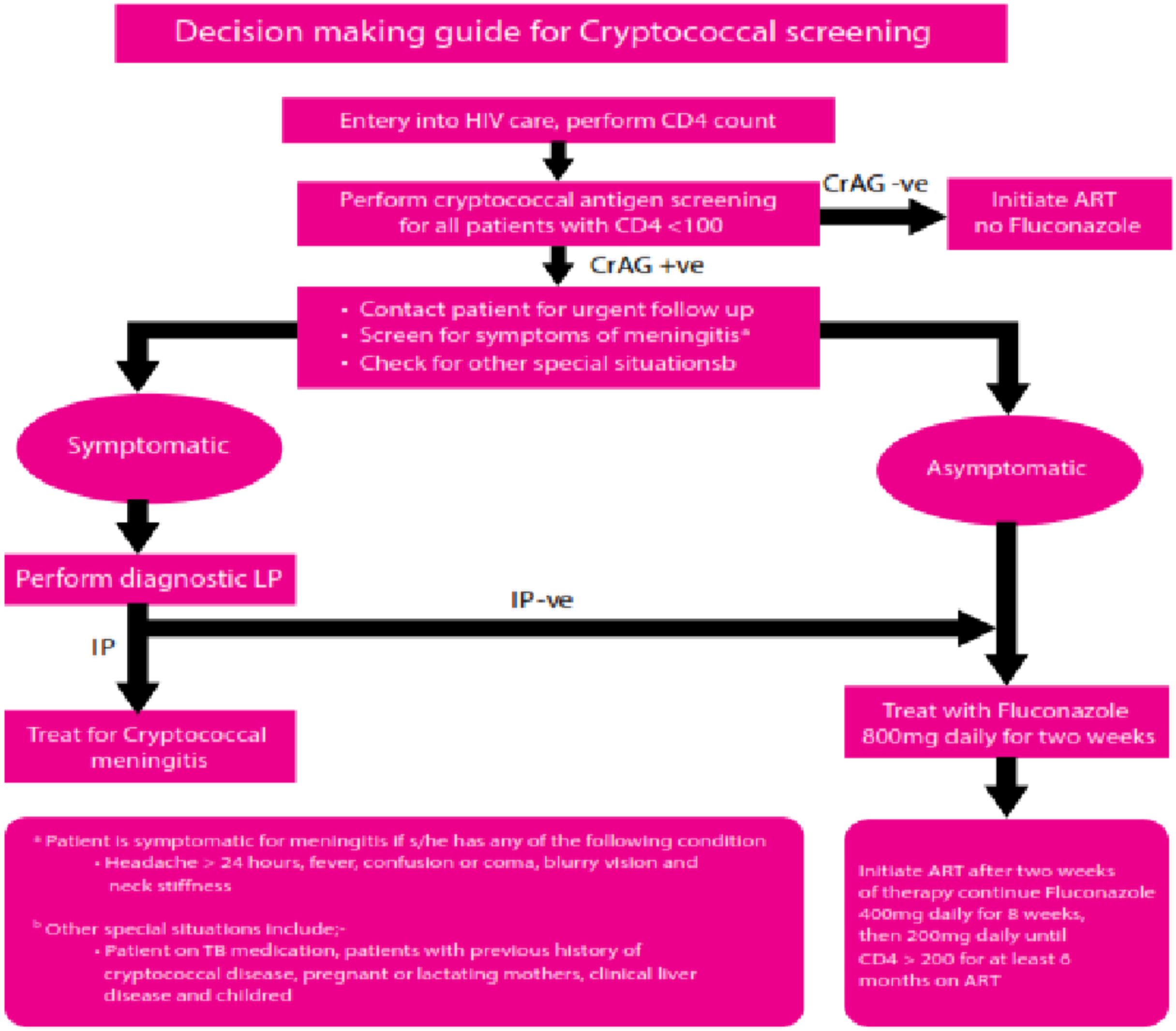
5.6.3.2 Cryptococcal meningitis

- ➢ Cryptococcal meningitis is particularly common in advanced immunodeficiency (CD4 count generally <100/mm3).
- ➢ It is a major contributor to high mortality before and after ART is initiated because of delayed presentation, together with poor availability and high cost of its treatment.
- ➢ Most HIV-associated cryptococcal infections are caused by Cryptococcus neoformans.
- ➢ Long-term steroid therapy, as well as other immunosuppressive medicines, is also risks for cryptococal infection.
- ➢ Typically, infection is acquired by inhalation of the fungus into the lungs.
- ➢ Cryptococcus is found in most warm climate, and is not restricted to the tropics.

Prevention of cryptococcal disease in people living with HIV

- ➢ The use of routine serum or Plasma cryptococcal antigen screening in ART-naive adults followed by pre-emptive antifungal therapy if screening is positive to reduce the development of cryptococcal disease, should be considered prior to ART initiation:
  - ✓ Where patients with a CD4 count less than 100 cells/mm3; and
  - ✓ Where this population also has a high prevalence (>3%) of cryptococcal antigenemia.

  - ✓ The following algorithm or decision-making guide shows how to decide whether a patient needs prophylactic fluconazole treatment to CrAg screening positive and asymptomatic patients with CD4 count less than 100cells/ml.
  - ✓ If the prevalence of cryptococcal disease is high in the locality (most likely in our setups), testing at CD4 count less than 200cells/ml may be preferred.
  - ✓ If the CrAg test is not available, prophylaxis might be warranted for patients with low CD4 count (<100 to 200cells/ml) in high-risk areas (>3% of cryptococcal antigenemia).


Decision making guide for Cryptococcal screening
Entery into HIV care, perform CD4 count
Perform cryptococcal antigen screening for all patients with CD4 <100
CrAG -ve
Initiate ART no Fluconazole
CrAG +ve
▪ Contact patient for urgent follow up
▪ Screen for symptoms of meningitis[a]
▪ Check for other special situationsb
Symptomatic
Asymptomatic
Perform diagnostic LP
IP-ve
IP
Treat for Cryptococcal meningitis
Treat with Fluconazole 800mg daily for two weeks

[a] Patient is symptomatic for meningitis if s/he has any of the following condition
  - Headache > 24 hours, fever, confusion or coma, blurry vision and neck stiffness

[b] Other special situations include;-
  - Patient on TB medication, patients with previous history of cryptococcal disease, pregnant or lactating mothers, clinical liver disease and childred

Initiate ART after two weeks of therapy continue Fluconazole 400mg daily for 8 weeks, then 200mg daily until CD4 > 200 for at least 6 months on ART

Fig; Decision-making guide for Cryptococcus screening

Clinical features

Sub-acute meningitis, with high mortality:

- In HIV-infected patients, cryptococcosis commonly presents as a sub-acute meningitis or meningoencephalitis with fever, malaise, and headache.
- Headache increasing over days to weeks, nausea, seizures, confusion, irritability, blurred vision, sixth cranial nerve palsy, papilloedema on retinal exam are common.
- Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only 1/4th to 1/3rd of patients.
- Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure, thought to result from impaired CSF absorption, or yeast infection of the brain.

- Coma or a reduced level of consciousness is associated with a poor prognosis.

Non- meningeal presentations of cryptococcosis include:

- Lung infections: pneumonia or chest pain and cough in a minority of patients, but often no fever.
- Skin lesions and lymphadenitis: Disseminated disease is associated with papular lesions with an umbilicated, centrally depressed area (similar appearance to molluscum contagiosum), which can become ulcerated.

Complications

- Chronic extensive genital HSV
- Raised ICP (increasing headache, vomiting, and cranial nerve palsy)
- Hydrocephalus, blindness, dementia, and personality change can occur as permanent sequelae.
- Cryptococcomas can develop in the brain, more commonly in patients who are not immunocompromised.
- Coma, cerebral oedema, and death follow if it is untreated, usually due to elevated ICP.

Investigations and diagnosis

- **LP** and CSF analysis
- Serology for cryptococcal antigens: If it is not possible or contraindicated to do LP, serum cryptococcal antigen can be used for diagnosis.
- CXR to demonstrate the organism

Management

- Requires hospitalization and evaluation by physician.
- The treatment is aimed at suppressing fungal growth and preventing squeal related to increased ICP.

Non-Pharmacologic

- Control of raised ICP: **daily LP with withdrawal of 20-30ml of CSF**
- Coma care (including NG tube feeding) if the patient is unconscious

Pharmacologic

Phases of management: Induction for 2 weeks followed by consolidation for 8 weeks

Options	**Induction (2 weeks)**	**Consolidation (8 weeks)**	**Maintenance (or secondary prophylaxis)**
Option A	➢ (High dose) Fluconazole 600 mg BID (In children 12mg/kg/dose BID)	Fluconazole 800 mg/day (children 12mg/kg/day)	Fluconazole 200 mg daily (children 6mg/kg/day)

	Plus ➢ Flucytosine, 25 mg/kg, PO, QID		
Option B*	➢ Amphotericin, 0.7 - 1 mg/kg/day Plus ➢ fluconazole 800 mg/day OR ➢ Flucytosine, 100mg/kg	Fluconazole 400 - 800 mg/day	

- ☛ ** If amphotericin used laboratory monitoring and pre-hydration is recommended.*
- ☛ ** If the patient has meningitis or pneumonia, treatment with a regimen containing amphotericin is preferred provided that facilities allow appropriate monitoring (kidney function and electrolytes).*

- Minimize acute infusion reactions when amphotericin is given (e.g. Fever, chills, headache, hypotension) by the following ways;
  - ✓ Infuse the initial dose slowly over 3 - 6 hours.
  - ✓ Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute infusion reactions (and in whom continued treatment with amphotericin is essential).

- **Discontinuation of maintenance treatment (secondary prophylaxis):** when patients are **stable and adherent** to ART and anti-fungal maintenance treatment for **at least one year** and have a **CD4 cell count maintained at ≥ 200 cells/ mm3 (2 measurements 6 months apart).**
- **Restarting Maintenance Therapy:**
  - ○ If CD4 count declines to ≤100 cells/µL

Management of elevated ICP:

- >90% of death s in the 1st 2 weeks and 40% of deaths in 3rd to 10th weeks are due to increased ICP. Thus, it is a must to manage.
- **Daily serial LP** should be done by **drawing 20-30 ml of CSF** based on patient's clinical response.
- **Signs of ICP** (headache, altered mental status, meningismus and changing in hearing or vision) **should be closely monitored**, if possible opening pressure should be measured.
- There is **no role for acetazolamide, mannitol, or corticosteroids** to reduce ICP.

Timing of ART initiation: Delay initiation of ART

- ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy due to life-threatening IRIS risk and
- After 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with fluconazole, or
- After 4-6 weeks of induction and consolidation treatment with high-dose oral fluconazole regimen (four weeks with non-meningeal disease).

- NB: Corticosteroids should not be routinely used during induction therapy unless it is used for management of IRIS

Poor prognostic signs

- Extra CNS manifestation (especially pulmonary)
- Altered mental status
- Low CSF WBC count less than 20cells/µL
- High CSF cryptococcal antigen titer

5.6.3.3 Peripheral neuropathies

- Among the most common causes of painful legs in HIV infection (due to complication of HIV infection itself, of drug therapy, or of other metabolic or organ dysfunction or nutritional deficiencies).
- **Distal symmetrical sensory polyneuropathy is the most common presentation** but mono-neuropathies can also occur.
- The neuropathies associated with HIV can be classified as:
  - ✓ **Primary** → HIV-associated.
  - ✓ **Secondary** → causes related to medications (INH), OIs or organ dysfunctions.

Diagnosis

- **Diagnosis is almost always clinical** → **pain, tingling sensations, paresthesia or numbness**, **depressed or absent ankle reflex, decreased sensitivity to different modalities of sensation** and in severe cases, **difficulty in walking**. The feet and sometimes the hands are involved in symmetrical distribution.
- The diagnosis can be supported by electro diagnostic studies including electromyography **(EMG)** and nerve conduction studies **(NCS**) when available.
- Blood tests are frequently obtained to exclude other causes of neuropathy.

Treatment

- Avoid the offending agent if identified.
- Remove other drugs associated with peripheral neuropathy.
- Supplemental vitamin intake for all patients including concomitant administration **of pyridoxine with INH**.
- Adjuvants for pain management (such as **Amitriptyline, carbamazepine**) indicated for patients with pain and paresthesia.

Monitoring of events

- Recognize presence of peripheral neuropathy.
- Assess severity at each clinical visit.
- Avoid drugs causing neuropathy.

5.6.4 Cutaneous disorders related to RVI infection

- Early OIs manifestations of HIV infection frequently occur in the skin.
- Adverse drug reactions (e.g., Nevirapine reactions may be life-threatening) and noninfectious conditions (e.g., neoplasm) or unknown causes also lead to the skin disorders in HIV patients.
- Nevertheless, infections are commonly seen in clinical practice;

Clinical features

- **Pruritus is the most common dermatologic symptom** in HIV infected patients.
  - ✓ It can be localized indicating primary skin lesion, or generalized that may or may not indicate primary skin lesions.
  - ✓ In many patient's pruritus may be severe and may not be amenable to available therapy.
  - ✓ **The most common skin conditions associated with pruritus** in patients with HIV include the following:
    - Excessive dryness of the skin (Xerosis cutis)
    - Eczemas like seborrheic dermatitis or contact dermatitis
    - Folliculitis (may include S. aureus infection or hypersensitivity to insects)
    - Drug eruptions
    - Scabies
    - Intertrigo (Candida, tinea, herpes simplex)

Diagnosis

- In most patients, **diagnosis** of skin disorders with HIV disease can be established by examining the lesions, **clinically**.
- However, as immune deficiency advances it may be useful to use investigations such as **biopsy** to diagnose specific dermatosis or use **staining and culture** to diagnose specific infections.

Skin disorders in HIV disease

- Skin disorders in HIV patients can be due to **infections, neoplasm**, and **hypersensitivity to foreign agents including drugs**, **or to unknown causes**. Nevertheless, **infections are commonly seen** in clinical practice; refer to the following table:

Table: Common skin infections in HIV disease

Infections	Disease	Clinical Presentations	Treatment	Remark
Bacterial	Cellulitis	Poorly defined Erythema. Pus and crust at the site plus signs of inflammation.	➢ Amoxicillin 500 mg TID for 14 days or ➢ Erythromycin 500 mg QID if allergic to penicillin.	Mostly encountered lower extremities and often unilateral.

	Impetigo	Erythematous small papules usually limited to few lesions coalescing in to crusted plaques.	➢ Topical antibiotics ➢ Amoxicillin for extensive disease.	Usually a superficial lesion.
	Carbuncle	Nodular Lesion with extensions to the deeper Structure. Signs of Inflammation present.	➢ Cloxacillin 500mg QID for 10 days.	Involves the trunk as well as extremities.
Viral	HSV	➢ Painful vesicular lesion around mouth or genitalia. ➢ Recurrent and extensive, difficult to eradicate during advanced immune deficiency.	➢ Acyclovir 400mg,PO, TID, for 10 days. (In children 20 mg/kg/dose QID)	If Chronic (> one month) patient will benefit from immediate ART initiation if not on ART
	HZV	Painful and vesicular eruptions with dermatomal distribution. When healed, scar will remain.	Acyclovir 800mg 5X per day for 7 days. (Monitor RFT).	➢ **When it involves the eyes, it is a medical emergency.** ➢ **Do not give Acyclovir* if duration is >72 hours.**
	Warts / verrucae	Painless flat to raised warts over fingers or genitalia in advanced immune deficiency, they tend to be multiple and exophytic.	Podophyllin, Imiquimod, Cryotherapy and Consult experts	Premalignant and risk for cervical cancer.
	Molluscum Contagiosum	Umbilicated and raised facial lesions that tend to be very big during immunodeficiency state.	May not require therapy;	Contagious
Parasitic infestation	Scabies	Pruritic lesions ranging from pinpointed erythematous papules involving interdigital, axillae and groin areas to varying degrees of hyperkeratotic plaques associated with significant skin thickening and crusting.	**First line** ➢ **Permethrin 5%,** Thin films of cream applied to all areas of body from the neck down and is washed off after 8-14 hours. Repeat the same dose after a week **Alternative** ➢ **BBL (Benzyl benzoate Lotion),** applied to the entire body, neck to toe for 3 to 5 consecutive evenings. Bath should be taken before the first and after the last application. **Systemic:** ➢ **Ivermectin**, 200µg/kg stat, for Norwegian (crusted scabies) and resistant forms of scabies. And it is	

			ideal for institutional outbreaks. ➢ **Antihistamines (such as cetirizine 5 - 10 mg daily)** are given for pruritus ➢ **antibiotics such as cloxacillin** are given for bacterial superinfections ➢ Burrows are visible in mild infestations but in crust scabies may not be evident leading to misdiagnosis.
Fungus	Dermatophytosis	Superficial causing ringworm or athlete's foot	➢ Topical antifungal (such as ketoconazole cream) for limited skin affected. ➢ Fluconazole for extensive lesion 100mg daily for 10 days.
	Oral Thrush	White plaques on the buccal mucosa including the tongues that can be scraped off leaving red base. Can be associated with candida paronychia or intertrigo.	➢ Miconazole gel 2% apply BID ➢ Fluconazole 100 mg daily for 10 for recurrent or oropharyngeal thrush.
	Deep Fungal infection	Presentation varies from fungating nodules and tumors to ulcers and diffuse papulonodular disease	➢ Disseminated Cryptococcus can be confused for Molluscum contagiosum. ➢ Treat with **amphotericin induction and/ or fluconazole maintenance.**

5.6.4.1 varicella-zoster (Chicken Pox) /ጉድፍ/

- Varicella virus causes two distinct syndromes in humans:
  1. Chicken pox → a primary illness, which most often occurs in children and is relatively benign
  2. Herpes zoster → a second distinct syndrome, which occurs in older adults or immunocompromised hosts and is due to reactivation of the dormant virus in the nerves. Herpes zoster causes significantly intense and sometimes long-standing pain. Herpes zoster in a young person is highly predictive of HIV infection and is a WHO clinical stage 2 conditions.

Clinical features of chicken pox

- Prodrome of fever, malaise, nausea, “flu-like” illness. 2 - 5 days later a generalized, itchy rash appears.
- Rash → Crops of papules-vesicles, then crusted lesions appear all over, **sparing the palms and soles.**
- Lesions co-exist in different stages of progression; i.e. new papules appear when older lesions are already crusted. Intense itching occurs.

Complications

- Complications are more often if HIV acquire as adults, and particularly in pregnant.
- After the introduction of vaccine, the number of complications in children dramatically declined, although the most common complication has remained bacterial superinfections;
- complications included
  - ✓ Pneumonia
  - ✓ Skin and soft tissue infections (42 %)
  - ✓ Dehydration (11 %), and
  - ✓ Neurologic complications (9 %) → Encephalitis, Reye syndrome hepatitis or haemorrhagic syndromes
- Varicella complications acquired during pregnancy before 28 weeks’ gestation, will cause congenital abnormalities in the child (also called congenital varicella syndrome). If acquired around the time of birth, it can cause neonatal varicella, which carries a high rate of pneumonia and other complications.

Treatment

- Start treatment ASAP ideally in < 24 hours after symptom onset.
- For oral treatment, the value of starting after 24 hours is not well established

Anti-viral therapy

- **Acyclovir and its analogues (valacyclovir, famciclovir)** are effective for the treatment of primary varicella in both healthy and immunocompromised hosts
- It is recommended for all HIV-positive adults.
- **Duration of treatment is for 7-10 days. Consider longer duration if lesions resolve slowly**

Drug options

- ✓ **Acyclovir**
  - In adults including pregnant women:
    - Acyclovir, 800mg, PO, 5 times daily for 7 - 10 days.
  - In immunocompromised adults or those with disseminated disease:
    - Acyclovir, 10mg/kg, IV, TID for 7 - 10 days (high-dose oral acyclovir, if no IV available).

Or

- ✓ **Valacyclovir**, 1 g, PO, TID for 7 to 10 days or
- ✓ **Famciclovir**, 500 mg, PO, TID for 7 to 10 days

N.B.

☛ For ***Extensive cutaneous lesions or visceral involvement:***

- ✓ **Acyclovir**, 10 to 15 mg/kg/dose, IV, TID, until clinical improvement
- ✓ **Switch to oral famciclovir or valacyclovir (preferred) or acyclovir (alternative)** to complete a **10 to 14 days** course when formation of new lesions has ceased and signs/symptoms of visceral infection are improving

Supportive care

- ➢ The following general measures can be used for the symptomatic management of rash and fever, and can also help reduce the risk of developing certain complications:
  - ✓ **Antihistamines or calamine lotion** are helpful for the symptomatic treatment of pruritus.
  - ✓ **Paracetamol** should be used to treat fever, particularly in children.
    - **Non aspirin NSAID's** can also be used. However, some providers discourage NSAIDS because of the uncertain association with streptococcal superinfection.
    - **Salicylates should be avoided since aspirin has been associated with the onset of Reye syndrome** in the setting of a viral infection
  - ✓ Fingernails should be closely cropped to avoid significant excoriation and secondary bacterial infection.
  - ✓ Secondary bacterial infections may require antibiotics.

5.6.4.2 Herpes zoster (shingles) /አልማዝ ባለጭራ

Clinical features

- ➢ **Painful vesicular rash in a dermatomal distribution of a nerve supply that does not cross the midline.** Pain sometimes comes before the appearance of the rash. Vesicles form in groups and progress to crusted lesions after a few days.
- ➢ The rash is generally limited to one dermatome, but can occasionally affect two or three neighboring dermatomes.
- ➢ Some patients can also have a few scattered vesicles located at some distance away from the involved dermatome.

- Most common areas: trunk, particularly the flanks, and forehead. Can involve the eye and cause corneal scarring and blindness.
- HIV patients have more frequent multidermal involvement, involvement of the trigeminal nerve, presence of systemic symptoms, and have a higher risk of disseminated disease.
- Myelitis, meningitis, and encephalitis with headache, fever, neck stiffness, altered motor and sensory function.
- Guillain-Barre syndrome.
- See pictures from physical examination section of Approach part of this chapter above.

Complications

- **Blindness** due to corneal involvement.
- **Post-herpetic neuralgia**: chronic pain in the area where the lesions occurred that can last for months to years after the acute episode.

Treatment

- **The management of herpes zoster includes:**
    - ✓ **Antiviral therapy** → to hasten healing of cutaneous lesions and to decrease the duration and severity of acute neuritis. Whether antiviral therapy decreases the risk of post-herpetic neuralgia is unclear.
    - ✓ **Analgesia** for patients with moderate to severe acute neuritis.
    - ✓ **Local lesion care** with daily bathing with soap and water.
    - ✓ **Antihistamines or calamine lotion** may be used to reduce itching

Choice of Antiviral agent

- ✓ **Acyclovir**: 800 mg 5 times daily for 7 days or
- ✓ **Valacyclovir**: 1g, PO, TID for 7 days or
- ✓ **Famciclovir**: 500 mg, PO, TID for 7 days

N.B

- **Acyclovir is available in most setups of Ethiopia. Valacyclovir and Famciclovir are preferred over acyclovir because of dosage frequency to increase adherence but there is no clear difference in efficacy.**
- Acyclovir and its analogues (Valacyclovir, Famciclovir) are dependent upon renal function for clearance. So, **follow up with RFT and dose adjustment is needed in moderate to severe renal insufficiency.**

Recommendations about antiviral therapy timing

1. ≤ 72 hours after onset

- Antiviral therapy should be initiated within 72 hours of clinical symptoms of uncomplicated herpes zoster to maximize the potential benefits of treatment.
- The benefit of antiviral therapy appears to be greatest in patients older than 50 years of age, in whom the pain of zoster generally persists longer. Although the efficacy of antiviral therapy in patients less than 50 years of age has not

been as well studied, the risk of adverse events secondary to antiviral therapy is very low.

2. >72 hours after onset

- Administer antiviral therapy after 72 hours if new lesions are appearing at the time of presentation, as this indicates ongoing viral replication.
- However, the clinical utility of initiating antiviral therapy more than 72 hours after the onset of lesions in immunocompetent persons is unknown.
- There is likely minimal benefit of antiviral therapy in the patient who has lesions that have encrusted.

3. Immunocompromised hosts

- **Antiviral therapy should be initiated** in all immunocompromised patients with herpes zoster, **even if they present after 72 hours**.
- Rapid initiation of therapy is particularly critical in the severely immunocompromised patient, such as the organ transplant recipient.
- **Immunocompromised hosts with disseminated zoster should be hospitalized for IV acyclovir therapy.**

Analgesia for acute neuritis

- Although antiviral therapy reduces pain associated with acute neuritis, pain syndromes associated with herpes zoster can still be severe.
- Use the following agents for the treatment of acute neuritis.
  - ✓ for **mild pain → NSAID's or paracetamol**, **either alone, or in combination** with a weak opioid analgesic (e.g. **codeine or tramadol**).
  - ✓ For **moderate to severe pain** that disturbs sleep → **stronger opioid** analgesics (e.g. **oxycodone or morphine**) may be necessary.

For Secondary bacterial infection

- Appropriate **staphylococcal and streptococcal antibiotic coverage** in addition to antiviral therapy.
- Patients should also be counseled to contact their clinician if they observe increased **erythema, warmth, or purulence surrounding any lesions, which could suggest secondary bacterial skin infection.**

Adjuvant therapies

- *Unless there is neuropathic pain or post herpetic neuralgia, For patients with uncomplicated zoster,* ***there is no role for adjuvant agents, such as gabapentin, TCA (like amitriptyline), or glucocorticoids****, in the acute setting.*

Patient monitoring

- Serial patient monitoring should include standardized pain measures and frequent follow-up to assess efficacy in relief of symptoms

Recurrent zoster

- Patients with recurrent zoster should be treated with antiviral therapy using similar a dose and duration as treatment of their initial episode.
- However, episodes of recurrent zoster are uncommon. Thus, viral cultures or other detection assays (eg, antigen or DNA detection) if available, should be performed since some patients (eg, those who present with recurrent herpes simplex outside of the mouth or genital area) may be misdiagnosed as having recurrent zoster.
- There are no data regarding the potential benefit of zoster vaccine in this scenario.

Complicated zoster

- Certain immunocompetent patients with herpes zoster will present with ocular, otic, or neurologic manifestations.
- Such patients may require IV and/or prolonged therapy.
- In addition, there may be a role for adjunctive glucocorticoids in certain conditions.

A) Herpes zoster ophthalmicus

- a serious sight-threatening condition, has been linked to varicella zoster virus (VZV) reactivation within the trigeminal ganglion.
- Patients can develop conjunctivitis, episcleritis, keratitis, and/or iritis.
- Early diagnosis and treatment is critical to prevent progressive corneal involvement and potential loss of vision.
- For mild ophthalmic involvement, topical acyclovir, 3% eye ointment applied into the eye every 4 hours should be given.
- The standard approach to herpes zoster ophthalmicus includes
  - ✓ **Oral** antiviral therapy **(acyclovir, valacyclovir, or famciclovir)** to limit VZV replication plus
  - ✓ Adjunctive **topical steroid drops** to reduce the inflammatory response and control immune-associated keratitis and iritis.
  - ✓ Parenteral **acyclovir (10 mg/kg, IV,TID for 7 days)** should be administered **if the patient is immunocompromised or requires hospitalization for sight-threatening disease**.

B. Acute retinal necrosis

- For immunocompetent patients
  - ✓ **Acyclovir**, 10 mg/kg, IV, TID, for 10 to 14 days **followed by valacyclovir**, 1g, PO, TID, for approximately 6 weeks.
- Such patients should be managed in conjunction with an ophthalmologist to evaluate the need for intraocular therapy and/or vitrectomy.
- In addition, empiric systemic glucocorticoids may be considered, especially if there is decreased visual acuity secondary to inflammation or optic nerve involvement.
  - ✓ **prednisolone**, 1 mg/kg/day, PO and taper by 10 mg every 5 days.

C. Ramsay Hunt syndrome

- The major otologic complication of VZV reactivation, which typically includes the **triad of;**
  - ✓ **Ipsilateral facial paralysis**
  - ✓ **Ear pain, and**
  - ✓ **Vesicles in the auditory canal and auricle.**
- Management
  - ✓ **Valacyclovir** 1g, PO, TID for 7 to 10 days **(if not available use acyclovir)** PLUS
  - ✓ **Prednisone,** 1 mg/kg for 5 days, without a tapering.
  - ✓ In severe cases (eg, vertigo, tinnitus, or hearing loss), IV therapy can be initiated, and the patient can then be transitioned to an oral antiviral agent when the lesions begin to crust.

D. Neurologic complications

- Neurologic complications where viral replication likely plays an important role (eg, symptomatic meningitis, encephalitis, and myelitis).
- Treatment
  - ✓ **Acyclovir**, 10 mg/kg, IV, TID, for 10 to 14 days

E. Postherpetic neuralgia

- The diagnosis is typically made when **pain persists beyond four months in the same distribution** as a preceding documented episode of acute herpes zoster
- Additional factors supporting the diagnosis are:
  - ✓ Advanced age
  - ✓ Severe prodromal pain with acute herpes zoster
  - ✓ Severe preceding rash
  - ✓ Distribution in trigeminal or brachial plexus dermatomes
  - ✓ The presence of allodynia
- Management
  - ✓ Tricyclic antidepressants (e.g. Amitriptyline), gabapentin, and pregabalin are generally the drugs of first choice.
  - ✓ **Amitriptyline** 25 - 50mg before bed for neuropathic pain and post-herpetic neuralgia

Preventing transmission to others

- Varicella and zoster are vaccine preventable diseases caused by VZV (MMRV vaccine)
- VZV is transmitted from person to person by direct contact or by aerosolization of virus from skin lesions.
- In general, VZV is much less transmissible from a person presenting with herpes zoster than from a person presenting with varicella.
- Patients with localized zoster are not infectious before vesicles appear and are no longer infectious when the lesions have re-epithelized.

- For those with active lesions, there are no specific precautions within the community setting. However, patients should be counseled about the risk of viral transmission to others. In addition, until the rash has crusted, patients should be advised to:
  - ✓ **Keep the rash covered, if feasible, and to wash their hands often to prevent the spread of virus to others.**
  - ✓ **Isolation of the patient to avoid spreading the virus. Contact should be avoided until all lesions are crusted over → Avoid contact with pregnant women who have never had chickenpox or the varicella vaccine, premature or low birth weight infants, and immunocompromised individuals.**

5.6.4.3 Pruritic papular eruption (PPE)

- Its prevalence ranges from 12 - 46% and it is uncommon in HIV negatives (PPV of 82 - 87%, and may play role in diagnosing HIV).

Clinical presentation and diagnosis:

- Intensely pruritic, discrete, firm papules with variable stages of development and predilection for extremities, though it can involve trunk and face.
- Excoriation results in pigmentation, scarring and nodules.
- In extreme form, eosinophilia and eosinophilic infiltrates of the skin are present.
- Severity of rash often correlates with CD4 count.
- Look at pictures under physical examination section from approach part of this chapter above

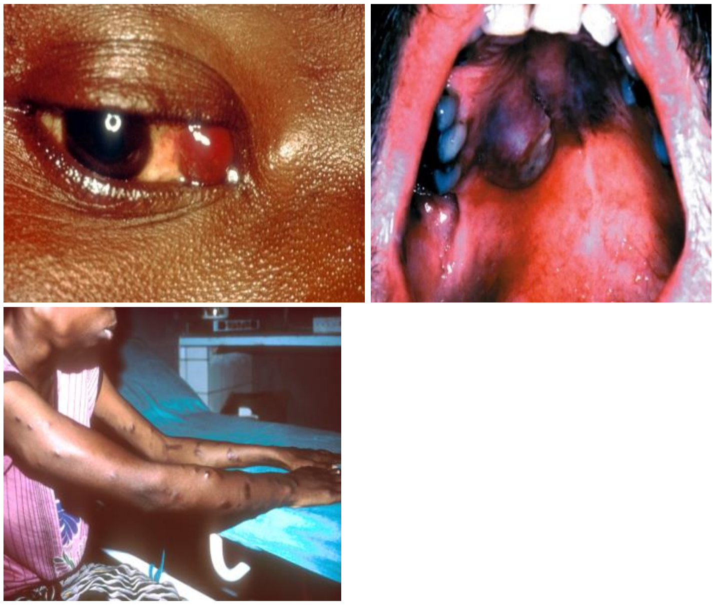
Treatment:

- Topical steroid and oral antihistamines.
- If refractory (often), short course prednisolone may be used.
- ART is often effective.

5.6.5 Kaposi sarcoma (KS)

- A multicentric neoplasm consisting of **multiple vascular nodules** appearing in the **skin, mucous membranes, and viscera**
- **AIDS defining malignancy**. Can occur at any CD4 count
- **Variants**:
  - ✓ AIDS related/ epidemic KS
  - ✓ Endemic/ African
  - ✓ Organ transplant related
  - ✓ Classic
- ☛ Aetiology → HHV-8 or KS associated HSV
- ☛ Manifestation
  - ✓ Pink /brown/ purple cutaneous and or mucosal papule or plaque.

  - ✓ It can appear anywhere in the body and often is symmetric (skin/ mucous membrane, GI, chest)



Pictures; KS in Eye, oral mucosa and skin over the hands

- ➢ Can occur as IRIS
- ➢ **DDx**
  - ✓ Purpura, hematomas, angiomas, dermatofibromas, or nevi
  - ✓ Bacillary angiomatosis, skin lymphoma, sarcoidosis, …
- ➢ **Dx** → biopsy
- ➢ **Staging**:

Good risk (stage 0)	Poor risk (stage 1)
➢ Skin, LN, minimal mucosa involvement ➢ CD4 > 200, ➢ No B symptoms ➢ No OI's ➢ Good performance status (Karnofsky >70)	➢ Extensive lesions, associate edema or ulcer ➢ CD4 < 200 ➢ B symptoms present ➢ Presence of other OI ➢ Poor performance status.

Treatment

- ➢ ART
- ➢ Local therapy → cryotherapy, laser, intralesional vinblastin, local radiation
- ➢ Systemic chemotherapy → indicated for rapidly progressive, severe lymphedema, pulmonary and other visceral involvement
  - ✓ Regimen → adriamycin, beomycin, vincristin every 2-3 weeks for 6 cycle.
  - ✓ Liposomal daunorubicin/doxorubicin, paclitaxel have better response rate

5.6.6 RVI - VL co infection

Refer from Leishmaniasis (click here → RVI - VL co infection)

Chapter 6; Stroke (የጭንቅላት ደም ስር በሽታ፣ እስትሮክ)

Dr. Mulualem. G

Clinical features and how to write hx of stroke patient

History

- **Pt's may present with**
    - Right or left sided body weakness
    - Failure to communicate
    - LOC
- **If a known Hypertensive patient** → ask the following on your hx
    - For how long he/she was Diagnosed to have hypertension
        - e.g a known hypertensive pt for the past 3 years or you can say 5 years back he/she was told to have hypertension (you can ask what was the presentation at that time and how Dx was made… no need to write on your HPI)
    - What medication he/she was taking… e.g he/she was on Amlodipine, HCT, spironolactone... ask dose and frequency of each drug, advised to stop alcohol and on salt restriction
    - Adherent or not
    - Where was the follow up and frequency (every month, every two months….)
    - How was his/her smx's in between… improving, worsening or no change at all… if not improving or worsening what was the reason (non-adherence, wrong diagnoses…)
- Ask handedness of the pt (Right or left-handed)
    - Speech area is in the dominant hemisphere. If there is derangement of speech, the dominant hemisphere is high likely to be the affected one.
    - 90% of right-handed persons are left dominance and 50% of left-handed persons are left dominant
- Right or left sided body weakness (i.e. both upper and lower extremity weakness of one side of the body)
    - It can be expressed as failure to use right/left upper and lower extremities.
    - Sudden onset (maximal at onset) or progressive onset which worsen until limb becomes flaccid/rigid based on the type of stroke
    - Happens while pt is awake and working his/her daily activities in hemorrhagic stroke (e.g. failed to hold meal while trying to eat, failed

    suddenly during farming etc.). Noticed while he/she awake from sleep or happen on his/her bed time in ischemic stroke
    - Starts from UL to LL or the reverse. Or may involve both upper and lower extremities at a time to the extent s/he failed to stand or can't raise, flex, extend by him/herself
- Speech disturbance → Broca's or Wernicke's aphasia which indicate MCA involvement
    - Aphasia
    - Difficult to communicate or difficulty of understanding/ may understand only gesture
    - There may be associated failure to swallow
    - If there is blurring of vision, decreased hearing ability in one or both sides → PCA is involved
- LOC, confusion
- Vomiting → may precede LOC and it is a sign of increased ICP
    - Projectile, nonbilious, nonblood tingled, non-foul-smelling vomiting of ingested matter/other, X-Y times per day
- Face deviation to the opposite side or to the same side of weakness
    - To the opposite side of weakness → uncrossed hemiparesis/plegia
    - To the same side of weakness → crossed hemiparesis/plegia
- Headache and neck stiffness
    - Globalized type of headache, relieving and aggravating factors
    - May be sudden and severe → ''the worst headache ever'' in SAH
- Abnormal body movement → indicates cerebellar involvement
    - Starts abruptly
    - With or without warning manifestations
    - Generalized/partial
    - With up rolling of the eyes and drooling of saliva
    - Followed by excessive salivation, bleeding from tongue (tongue bite), urinary or fecal incontinence (observed by one of family members)
    - Finally, LOC → ask duration of LOC which is mostly less than 5 minutes
- Fecal or urine incontinence → indicates ACA involvement

Hemorrhagic stroke	Ischemic stroke
✚ Gradual in onset→ progressive worsening of smx's ✚ Associated with decreased level of consciousness (LOC) ✚ +ve features of increased ICP → projectile vomiting, headache, papilledema on P/E ✚ Stroke happening at stressful conditions and pt is awake like farming, sexual activity etc. ✚ **HTN, High alcohol intake** and smoking favors hemorrhagic stroke but can be RF for Ischemic stroke also. ✚ **ICH** are characterized by premonitory symptoms like headache; nausea and vomiting; onset is sudden with rapid progression of neurologic features over hours; often associated with loss of consciousness; often occur during strenuous activities	✚ Maximal at onset → severe FND at the onset ✚ No change in mentation ✚ No features of increased ICP ✚ Happens at rest or during sleep time → i.e. usually noticed in the morning ✚ RF that favors ischemic stroke include ✓ DM ✓ CHF (atrial fibrillation) resulting in cardioembolic stroke ✓ Previous MI and PAD ✚ **Embolic strokes** occur often when patients are awake; the weakness is often **maximal at onset** and hardly progress thereafter; the neurologic deficits are often severe as the infarcts are very large; often follows TIA. ✚ **Thrombotic strokes** start suddenly but neurologic deficits are stuttering and progresses relatively slowly; often stroke occur during night while patients are asleep.

Risk factors for stroke

Modifiable RF	Non modifiable RF
✚ HTN ✚ DM ✚ Dyslipidaemia ✚ Obesity and physical inactivity ✚ Alcohol intake ✚ Cigarette smoking ✓ A major risk factor for CAD, stroke, and PAD ✓ It is an independent risk factor for ischemic stroke in men and women of all ages, and a leading risk factor of carotid atherosclerosis in men: 2-3 times than non-smokers ✚ TIA ✚ Prior stroke ✚ CHF (especially atrial fibrillation, VHD, DCMP and IE which predispose to cardio embolic stroke)	✚ Old age ✓ An increasing age is the most powerful risk factor for stroke. ✓ The incidence of stroke doubles each decade past 55 years of age: Half of all strokes occur in people older than 75 years. ✚ Gender (M>F) ✓ Men age 45 - 75 develop ischemic strokes at higher rates than women; **thereafter**, stroke rates are **higher in women** ✓ Women has higher case fatality rates than men ✚ Race → common in African Americans ✚ Previous vascular event like MI, embolism

  - ✓ Atrial fibrillation, is the most common cause for cardio-embolic stroke, and it is a risk factor for future cardiovascular disease.
- CAD, PAD
- OCP use
- Hyperlipidemia (atherosclerosis)
- Anticoagulant therapy
- Hypercoagulable states (SCA, PCV, protein S &C deficiency, antithrombin III deficiency, SLE)
- Substance abuse like cocaine, amphetamine
- Trauma → carotid or vertebral artery dissection
- Spinal manipulation → vertebral artery dissection
- Genetic disorders like EDS and marfan syndrome → increased risk of vascular dissection to result SAH.
- Family hx

N.B **ABCD^2 score**

ABCD^2	Score
A → age > 60	1
B → BP ≥ 140/90	1
C → Clinical smx like ☛ Unilateral weakness------- ☛ Speech disturbance-------	 2 1
D → duration ☛ Lasting ≥ 60 minutes ---- ☛ < 60 minutes --------------	 2 1
D → DM	1
Total	9
ABCD2 scores of ≥ 4 indicate a moderate to high stroke risk and justify prompt hospital admission	

Complication of stroke

Early complications

- ✓ Cxn due to immobility
  - Infection like pneumonia
  - Aspiration from LOC
  - Pressure sore
  - Painful shoulder
  - Venous TE like DVT and PE
  - UTI/constipation
- ✓ Cxn due to cortical brain injury
  - Cerebral edema and hemorrhage
  - Seizure
- ✓ Fall down injury during the attack

Late complications

- ✓ Contracture or spasticity
- ✓ Neurologic disability or paralysis like wheelchair dependent
- ✓ Epilepsy
- ✓ Aphasia
- ✓ Sleep disturbance
- ✓ Socioeconomic factor related to difficulty in involvement of daily activity and permanent need of help from family members
- ✓ Depression/anxiety from prolonged immobility

Sample history

Sample history of a patient from debark with Emergency ward DX of Right sided, crossed, flaccid hemiplegia 2ry to ischemic stroke 2ry to uncontrolled HTN r/o hemorrhagic stroke

Chief compliant

Failure to use right upper and lower extremities of 4 hr's duration

HPI

This is a Right-handed, known hypertensive patient for the past 3 years on amlodipine to be taken 10 mg po daily and Hydrochlorothiazide to be taken 25 mg po daily, advised to stop alcohol and on salt restriction. He was Adherent for his medication with regular follow up at debark general hospital every two to three months.
Currently presented with Sudden onset right sided body weakness of both upper and lower extremities of 04 hours duration. The weakness happens on his bed time in which he noticed while he awakes from sleep. It was maximal at onset involving both upper and lower extremities at a time to the extent he failed to stand from sleeping position and can't raise, flex or extend his right-side extremities by himself.

Two hours before admission he experienced failure to communicate but he was able to understand only gesture associated with face deviation towards the right side but no LOC, vomiting or headache

While they were coming to our hospital by ambulance (approximately 30 minutes before admission), he experienced single episode of sudden onset, generalized Abnormal body movement together with up rolling of the eyes and drooling of saliva followed by excessive salivation, bleeding from tongue and urinary incontinence (observed by one of family members in the ambulance), Finally he loses his consciousness and awakes approximately 3-4 minutes later.

For this, he visited debark general hospital where he was catheterized, glucose level measured, put on intranasal oxygen, resuscitated with half bag of NS and referred to our hospital for better investigation and management.

- No hx of DM *(RF)*
- No hx of Dyspnoea, orthopnoea, PND, palpitation *(cardioembolic stroke from cardiac causes)*
- No hx of head trauma *(RF, or DDX in SDH)*
- No hx of Smoking or chronic alcohol intake *(RF)*
- No hx chat chewing or other drug use *(cocaine, amphetamine… for females consider OCP as hypercoagulable state)*
- No hx of malar rash, photophobia or joint pain *(SLE as RF)*
- No hx of gum bleeding, epistaxis or bleeding from other sites *(bleeding disorder may be the cause for haemorrhagic stroke, don't give heparin in bleeding disorders)*
- No hx of intermittent claudication or leg swelling *(DVT as cxn)*
- No hx of chest pain cough or fever *(pneumonia, PE as cxn)*
- No hx of constipation *(cxn)*
- No hx of Ear discharge, tooth extraction, or sinusitis *(brain abscess as DDX)*
- No Similar hx of illness in the family, previous hx of similar illness or transient weakness of extremities *(TIA, Hemiplegic migraine)*

Finally, he was admitted to our hospital ED carried by his families from ambulance.

Physical examination (pertinent findings)

1 GA

- Face deviation
- LOC (decreased level of consciousness)
- Limb position → Externally rotated limb (in flaccid hemiparesis/plegia), internally rotated limb (in spastic hemiparesis/plegia)
- Speech disturbance
- Cardio respiratory distress

2 Vital signs

- Irregularly irregular pulse → Atrial fibrillation
- HTN as RF, may be hypotensive
    - Hypotension is associated with worsening of stroke; can be associated with serious concomitant conditions like MI, aortic dissection or sepsis.
    - Hypertension is a normal response to stroke but malignant HTN should be treated.
    - Very high HTN may suggest ICH.
- Tachypnoea and tachycardia
- Febrile

3 HEENT

- Eye changes

- Retina → hollen horst plaque from amaurosis fugax (mono ocular blindness due to occlusion of ophthalmic branch of carotid artery), diabetic changes, Retinal emboli, hypertensive changes, arcus senilis

4 LGS

5 RS

- Chyne stocke breathing (deep and labored tachypnoea followed by apnoea)→ due to hemispheric cerebral oedema
- Pulmonary edema
- Pneumonia features (from aspiration pneumonia or infection)

6 CVS

- Bruit over the carotid artery and other major arteries
- Arrythmia (Abnormal pulse rhythm like irregularly irregular pulse from atrial fibrillation)
- CHF Features
- Cardiomegaly signs from longstanding HTN

7 Abdominal examination

8 GUS

- Bladder distension from urinary retention

9 MSS

- DVT (peripheral emboli) → limb ischemia
- Injuries sustained during collapse with stroke

10 IS

- Skin and mucous membrane bleeding features → bleeding disorders as a cause of ICH
- Xanthelasma, rash → arteritis, splinter haemorrhage, livido reticularis

11 NS

- Level of consciousness
    - May be comatose
- CN
    - **CN palsy**
        - ✓ **CN VII damage → Facial deviation**
            - **Infra nuclear if both upper and lower face area involved**
            - **Supranuclear if only lower face part involved**
    - Dilated pupil, decerebrate rigidity → **visual field examination is very important if posterior fossa haemorrhage is suspected**
    - Homonymous visual field defects
- Motor examination
    - Inspection → decreased muscle bulk of the affected limb, fasciculation
    - Palpation
        - ✓ Hyper/hypotonic→ i.e. spastic or flaccid weakness respectively
        - ✓ Decreased power
        - ✓ Hyperreflexia in spastic hemiparesis and hyporeflexia in flaccid hemiparesis

- Sensory examination
    - Sensory loss on the affected side → difficult to assess if comatose
- Meningeal irritation signs are usually -ve but there may be +ve
- Coordination
    - Construction apraxia (inability to perform learned activity e.g. writing)
    - Cortical sensory loss
        - ✓ Absent stereognosis
        - ✓ Agraphtesia
        - ✓ Absent two-point discrimination
        - ✓ Absent simultaneous extinction.

N.B

Very critical tests: swallow test; ocular muscles and gaze tests; mental status assessment and sensori-motor assessment

- ❖ ACA damage
- ❖ MCA damage
    - ✓ aphasia
- ❖ PCA damage
    - ✓ Dysarthria and facial numbness
    - ✓ Ataxia and hornor sxx
    - ✓ Facial weakness
    - ✓ Hemiparesis
    - ✓ Hemisensory loss
    - ✓ Hemianopia
    - ✓ comatose
- ❖ Thalamic hemorrhage
    - ✓ Down and inward deviation of eye
    - ✓ Unequal pupil with absent pupillary reflex
    - ✓ Ipsilateral horner sxx
    - ✓ Absent convergence
- ❖ Pontine hemorrhage
    - ✓ Deep coma with quadriplegia
    - ✓ Decerebrate rigidity with pinpoint pupil that react to light
    - ✓ Doll's head/oculocephalic manoeuvre

NIHSS (The National Institutes of Health Stroke Scale) score

- The NIHSS is a highly reliable and valid screening assessment for the rapid evaluation of a patient with acute stroke: Although it's not a substitute for comprehensive neurologic examination.
- The 11-item scale measures consciousness, orientation, visual fields, gaze, language fluency and comprehension, speech, sensory loss and neglect, motor strength, and limb ataxia.

- The scale can easily be completed in less than 10 minutes and serves as an initial measure of stroke severity ranging from **0 (no deficits) to 42 (maximum score)**
- **Minor stroke considered when NIHSS score is <5**
- NIHSS score emphasizes much on dominant hemispheric function than non-dominant functions
- Additionally, the NIHSS may underestimate posterior circulation stroke deficits compared to anterior circulation stroke deficits

Components of NIHSS score

- For clinical practice only, you are not obliged to rehearse it (you can use this text or UpToDate 2018 during scoring)

1. **A. Level of consciousness**

   ○ Alert (0 points)

   ○ Not alert, but arousable with minimal stimulation (1 point)

   ● Not alert, requires repeated stimulation to attend (2 points)

   ○ Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic (3 points)

   B. Patient knows month and own age

   ○ Answers both correctly (0 points)

   ○ Answers one correctly (1 point)

   ○ Both incorrect (2 points)

   C. Patient opens and closes eyes and grips and releases the nonparetic hand on command

   ○ Obeys both correctly (0 points)

   ○ Obeys one correctly (1 point)

   ○ Both incorrect (2 points)

2. **Best gaze (only horizontal eye movement)**

   ○ Normal (0 points)

   ○ Partial gaze palsy (1 point)

   ○ Forced deviation (2 points)

3. **Visual field testing**

   ○ No visual loss (0 points)

   ○ Partial hemianopia (1 point)

   ○ Complete hemianopia (2 points)

   ○ Bilateral hemianopia (blind including cortical blindness) (3 points)

4. **Facial Palsy /paresis/ (ask patient to show teeth or raise eyebrows and close eye)**
    - ○ Normal symmetrical movement (0 points)
    - ○ Minor paralysis (flattened nasolabial fold, asymmetry on smiling) (1 point)
    - ○ Partial paralysis (total or near total paralysis of lower face) (2 points)
    - ○ Complete paralysis of one or both sides (3 points)
5. **Motor function of arm**
    A. right arm
    - ○ No drift (0 points)
    - ○ Drift (1 point)
    - ○ Some effort against gravity (2 points)
    - ○ No effort against gravity (3 points)
    - ○ No movement (4 points)
    - ○ Untestable (amputation or joint fusion at the shoulder) (0 points)

    B. Motor function of left arm
    - ○ No drift (0 points)
    - ○ Drift (1 point)
    - ○ Some effort against gravity (2 points)
    - ○ No effort against gravity (3 points)
    - ○ No movement (4 points)
    - ○ Untestable (amputation or joint fusion at the shoulder) (0 points)
6. **Motor function of leg**
    A. right leg
    - ○ No drift (0 points)
    - ○ Drift (1 point)
    - ○ Some effort against gravity (2 points)
    - ○ No effort against gravity (3 points)
    - ○ No movement (4 points)
    - ○ Untestable (amputation or joint fusion at the hip) (0 points)

    B. left leg
    - ○ No drift (0 points)
    - ○ Drift (1 point)
    - ○ Some effort against gravity (2 points)

- ○ No effort against gravity (3 points)
- ○ No movement (4 points)
- ○ Untestable (amputation or joint fusion at the hip) (0 points)

7. Limb ataxia

- ○ Absent (0 points)
- ○ Present in one limb (1 point)
- ○ Present in two limbs (2 points)
- ○ Untestable (amputation or joint fusion) (0 points)

8. Sensory to pinprick or withdrawal from noxious stimulus

- ○ Normal (0 points)
- ○ Mild-to-moderate sensory loss (1 point)
- ○ Severe-to-total sensory loss (2 points)

9. Language

- ✓ ○ No aphasia (0 points)
- ○ Mild-to-moderate aphasia (1 point)
- ○ Severe aphasia (2 points)
- ○ Mute, global aphasia (3 points)

10. Dysarthria

- ○ None (0 points)
- ● Mild-to-moderate dysarthria (1 point)
- ○ Severe dysarthria (2 points)
- ○ Intubated or other physical barrier to producing speech (0 points)

11. Extinction and inattention

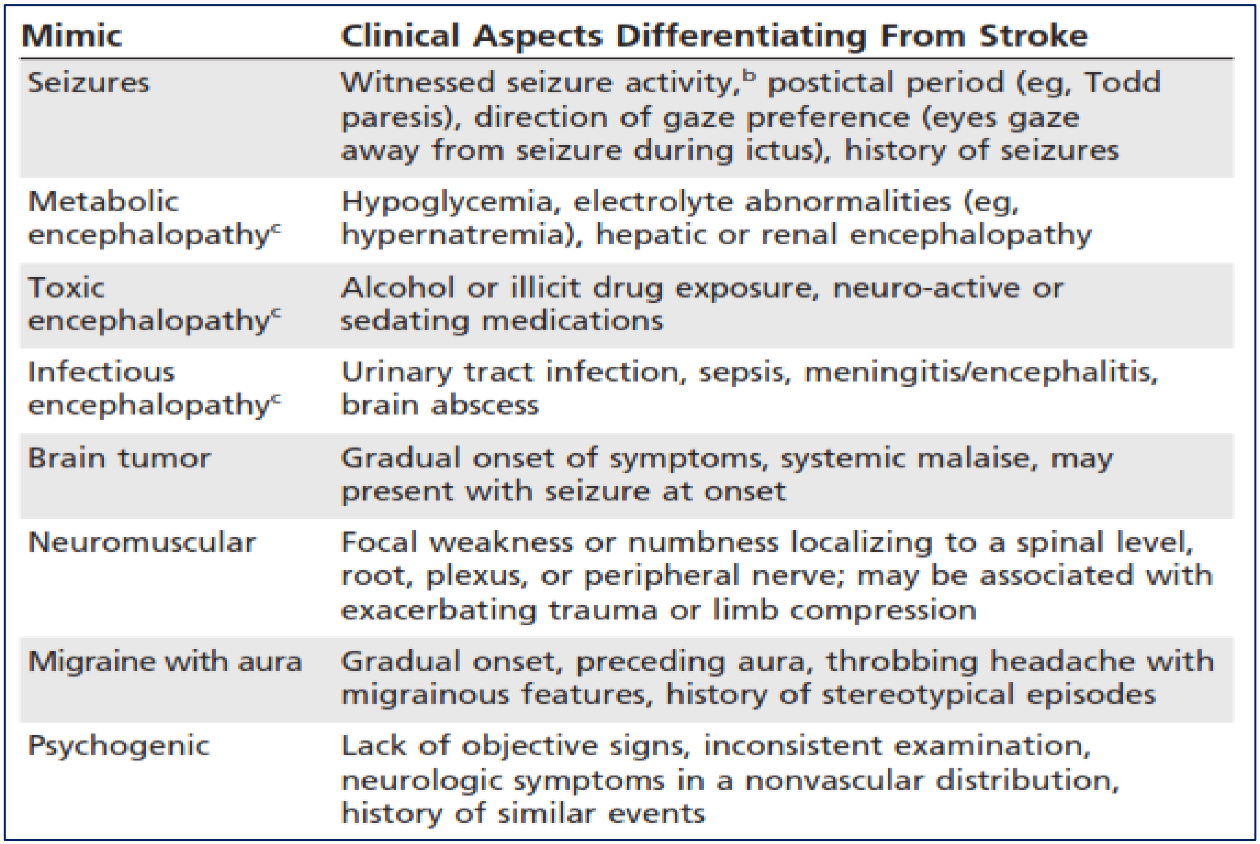
- ● No abnormality (0 points)
- ○ Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities (1 point)
- ○ Profound hemi-inattention or extinction to more than one modality (2 points)

DDX

1) Stroke
   - Hemorrhagic stroke
     - ✓ ICH
     - ✓ SAH
   - Ischaemic stroke
     - ✓ Embolic
     - ✓ Thrombotic
2) Vasculitis
   - ✓ TB
   - ✓ Syphilis
   - ✓ SLE
3) Bleeding to brain tumour→ characterized by seizure, hydrocephalus, acute neurologic features like FND
   - ✓ Glioblastoma multiforme
   - ✓ Metastasis tumour to brain from melanoma, Bronchogenic ca, RCC
4) Acute SDH
5) Neurosyphilis
   - ✓ Vasculitis
   - ✓ Syphilitic guma
6) Todd's paralysis → a.k.a post ictal paralysis. paralysis which occurs following seizure
7) Hemiplegic migraine
8) Encephalopathy
   - ✓ Metabolic → hepatic encephalopathy, ureamic encephalopathy
   - ✓ Toxic → alcohol, illicit drugs
   - ✓ Infectious → meningoencephalopathy, sepsis
9) Brain abscess
   - Triads of brain abscess include **fever, headache, FND**
10) Neurocysticercosis
    - ✓ Rare in Ethiopia since pork is not usual food due to cultural and religious values
11) Space occupying lesions
    - ✓ Take long time course unlike stroke

Stroke mimics

STROKE is considered when focal deficits occurs abruptly and follow vascular territory



Mimic	Clinical Aspects Differentiating From Stroke
Seizures	Witnessed seizure activity,[b] postictal period (eg, Todd paresis), direction of gaze preference (eyes gaze away from seizure during ictus), history of seizures
Metabolic encephalopathy[c]	Hypoglycemia, electrolyte abnormalities (eg, hypernatremia), hepatic or renal encephalopathy
Toxic encephalopathy[c]	Alcohol or illicit drug exposure, neuro-active or sedating medications
Infectious encephalopathy[c]	Urinary tract infection, sepsis, meningitis/encephalitis, brain abscess
Brain tumor	Gradual onset of symptoms, systemic malaise, may present with seizure at onset
Neuromuscular	Focal weakness or numbness localizing to a spinal level, root, plexus, or peripheral nerve; may be associated with exacerbating trauma or limb compression
Migraine with aura	Gradual onset, preceding aura, throbbing headache with migrainous features, history of stereotypical episodes
Psychogenic	Lack of objective signs, inconsistent examination, neurologic symptoms in a nonvascular distribution, history of similar events

Final Ass't example

Right/left sided, Crossed/uncrossed, spastic/flaccid, hemiparesis/plegia, 2ry to ischaemic/hemorrhagic stroke 2ry to cardio embolism/HTN/DM….

N.B.

- Face deviation to the opposite side of weakness → **uncrossed** hemiparesis/plegia
- Face deviation towards the same side of weakness → **crossed** hemiparesis/plegia
- **Spastic** → limb rotated inward and hypertonic
- **Flaccid** → limb rotated outward and hypotonic

Then localize the lesion as supra/infranuclear (i.e cortical or subcortical) → *refer paraplegia of Nitsbin (click here →* Localization of neurologic disorders *)*

IX

N.B for stroke pt's, before going to the list of Ix modalities Do RBS, manage life threatening conditions, stabilize the patient, then do emergency CT. After that, you will go to other IX and mgt concomitantly.

'Time is brain'

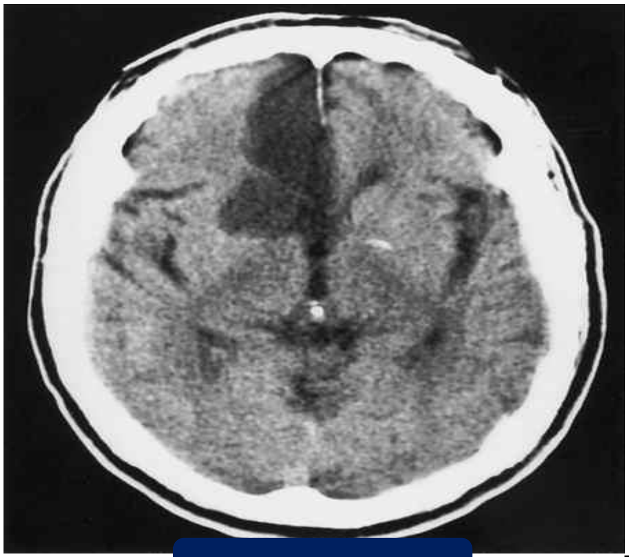
1. Perform RBS
   If suspected bleeding risk; CBC, PT, PTT
2. Perform CT
3. Start rTPA if indicated

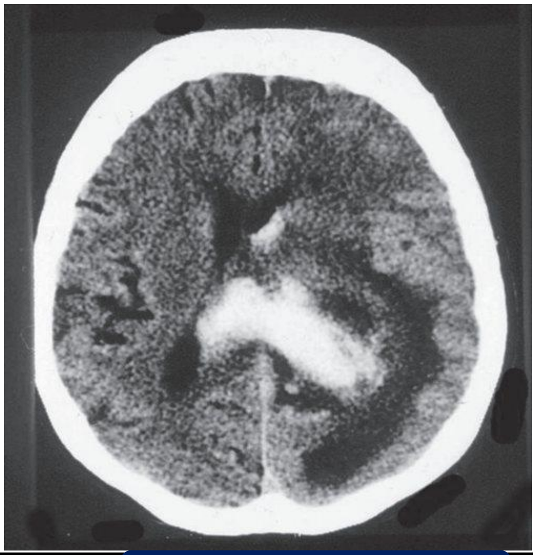
1. **RBS & FBS**
   - ✓ To r/o hypoglycemia
   - ✓ DM is RF for stroke
   - ✓ FBS Should be between 140 and 180
     - ▪ If FBS is < 50 or > 400, thrombolytic (t-PA) is contraindicated
2. CBC & ESR
   - ✓ PCV, hypercoagulable state from SLE
   - ✓ Leukocytosis from infection
3. **Lipid profile**
   - ✓ Hyperlipidemia (dyslipidemia is RF for stroke)
4. **PT & PTT**
   - ✓ For mgt purpose → to give heparin based on bleeding tendency
   - ✓ Hypercoagulable states (thromboembolism)
   - ✓ Hemorrhagic stroke from bleeding tendency
5. PICT
6. OFT → like LFT, RFT to prevent 2ry brain injury
7. Serum electrolyte level
   - ✓ Hyponatremia (cerebral salt wasting sxx) in SAH
   - ✓ Cerebral edema in hyponatremia
   - ✓ Hypernatremia in metabolic encephalopathy → DDX
8. Syphilis serology (VDRL in our set up)
9. Blood culture→ if IE is suspected
10. ANA → for SLE

Imaging

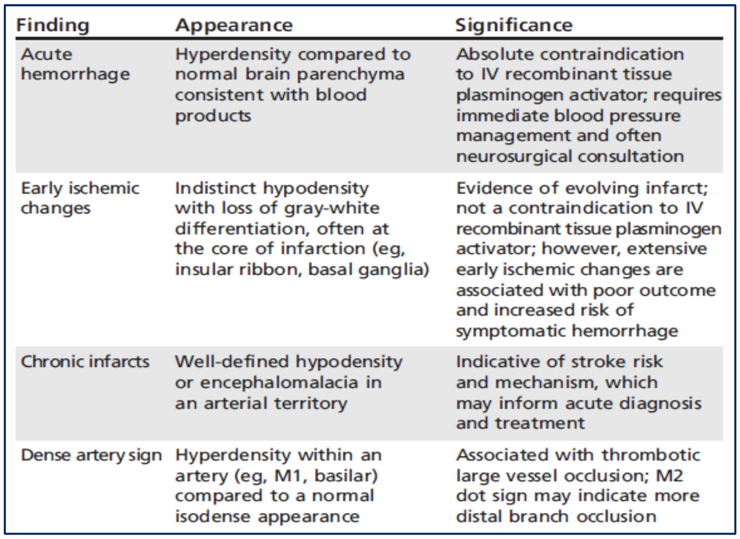
11. **CT scan**
    - ✓ CT is preferred than MRI in first cases of stroke

- ✓ Mandatory initial Ix which should be done immediately on patient arrival. **Time** took from initial evaluation to door of CT scan **should not exceed 30 minutes** (but difficult to do immediately in our setup)
- ✓ **Haemorrhagic** stroke appears **hyperdense** since blood have iron content
- ✓ **Ischaemic** stroke appears **hypodense**
- ✓ More sensitive than MRI for hemorrhage
- ✓ Infarcts may not appear with in 48 hr's
- ✓ After differentiating the type of stroke by emergency CT scan search for the cause based on available Ix's (Doppler carotid scan, MRA/CTA, cerebral arteriography, PET/SPECT scan)

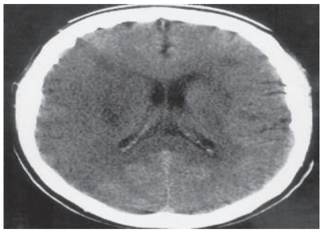

ISCHEMIC STROKE


HEMORRHAGIC STROKE

Watch for early signs of ischemia in CT scan



Finding	Appearance	Significance
Acute hemorrhage	Hyperdensity compared to normal brain parenchyma consistent with blood products	Absolute contraindication to IV recombinant tissue plasminogen activator; requires immediate blood pressure management and often neurosurgical consultation
Early ischemic changes	Indistinct hypodensity with loss of gray-white differentiation, often at the core of infarction (eg, insular ribbon, basal ganglia)	Evidence of evolving infarct; not a contraindication to IV recombinant tissue plasminogen activator; however, extensive early ischemic changes are associated with poor outcome and increased risk of symptomatic hemorrhage
Chronic infarcts	Well-defined hypodensity or encephalomalacia in an arterial territory	Indicative of stroke risk and mechanism, which may inform acute diagnosis and treatment
Dense artery sign	Hyperdensity within an artery (eg, M1, basilar) compared to a normal isodense appearance	Associated with thrombotic large vessel occlusion; M2 dot sign may indicate more distal branch occlusion



CT IS important for

1. Large-artery atherosclerotic disease resulting in stenosis or occlusion,
2. Small-vessel or penetrating artery disease (lacunes)
3. Cardiogenic or artery-to-artery embolism,
4. Non-atherosclerotic vasculopathies,
5. Hyper-coagulable disorders
6. Infarcts of undetermined causes

12. MRI

- ✓ Useful to delineate ischemic strokes, especially involving the brainstem or cerebellum, or lacunar strokes,
- ✓ Diffusion, perfusion, and gradient echo MR sequences can rapidly detect early ischemic and hemorrhagic lesions
- ✓ Describe the amount of at-risk tissue (the "ischemic penumbra")

13. ECG & ECHO

- ✓ Arrythmia
- ✓ Recent MI
- ✓ IE (vegetation), thrombus, cardiac shunt (paradoxical embolism)
- ✓ For mgt purpose → don't elevate BP if there is MI and stroke together

14. Carotid and Aortic doppler U/S

- ✓ Describe the nature of the vessel and assess the presence of atheroma or thrombi
- ✓ Better with carotid angiography

15. CXR → cardiomegaly from longstanding HTN
16. MRI based angiography (MRA) → can detect stenosis of the artery, giant aneurysm, arterial dissection

Discussion

Look at neurolocalization before the discussion of stroke for better understanding (click here → Localization of neurologic disorders)

Stroke

- Cerebro-vascular diseases include some of the most common and devastating disorders collectively called as **Stroke**
- **A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause.**
- Include Ischemic stroke, Hemorrhagic stroke, and Cerebro-vascular anomalies such as intracranial aneurysms and AVMs (Arteriovenous malformations).
- All of which manifest with an abrupt onset of neurologic features that are often focal in nature: Often follow vascular distributions.
- Focal ischemia or infarction is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart.
- A generalized reduction in cerebral blood flow due to systemic hypotension (e.g., cardiac arrhythmia, MI or hemorrhagic shock) produces Syncope.
- If low cerebral blood flow persists for a longer duration, then infarction in the border zones between the major cerebral artery distributions may develop: **Watershed ischemia**
- Intracranial hemorrhage (ICH) is caused by bleeding directly into or around the brain; it produces neurologic deficit by mass effect, blood toxic effect or increased ICP

Stroke: Classification

1. **Ischemic Stroke**

- Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies because of either an in-situ thrombosis formation or an embolus showered from the heart or proximal arteries

  1.1 **Embolic:** Cardio embolic or arterio-arterial emboli; Paradoxical embolism
  1.2 **Thrombotic:** Thrombosis formation in intra cranial vessels themselves

2. **Hemorrhagic Stroke**

- Acute bleeding into intra cranial structures generally called intra-cranial hemorrhage.
- Based on the location of bleeding: Intra-paranchymal; SAH; SDH; EDH; IVH

6.1 Ischemic stroke

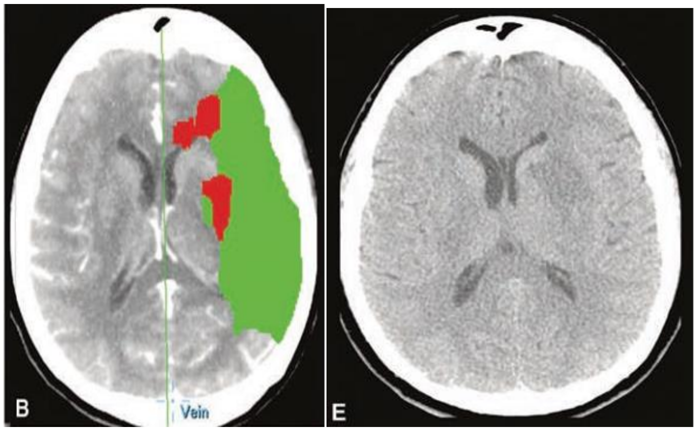
Epidemiology

- ✓ Stroke is the second leading cause of death worldwide
- ✓ Every 40 seconds there is an occurrence of stroke in USA.
- ✓ Some 88% of these strokes are ischemic. Around 18-20% of stroke is due to ICH
- ✓ In developing areas, the Incidence rate of ICH is relatively higher
- ✓ In UOG Hospital; among stroke patients admitted to the Hospital, 60-70% are due to Ischemic stroke commonest cause being arterio-arterial embolic stroke
- ✓ Steep decreases in stroke incidence and mortality have occurred in industrialized nations.
    - This is attributed to a declining stroke incidence, and lower case-fatality rates, with suggestive evidence favoring a trend in declining stroke severity.
    - However, the declining stroke incidence has been reversing with the aging of the population, greater awareness of stroke symptoms, and better diagnostic tools
- ✓ Stroke mortality and incidence are increasing in developing nations.
- ✓ Socioeconomic factors, dietary and lifestyle behaviors, different patterns of risk factors, and environmental conditions may explain the different incidences of stroke observed in different parts of the world
- ✓ Increased life expectancy; improved awareness and improved diagnostic facilities contribute to increase in incidence rate

Pathophysiology of ischemic stroke

- ❖ Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies.
- ❖ The magnitude of flow reduction is a function of collateral blood flow, and this depends on;
    - ✓ Individual vascular anatomy (which may be altered by disease) i.e. Collateral supply
    - ✓ The site and extent of occlusion
    - ✓ Systemic blood pressure.
    - ✓ The duration of ischemia
        - ▪ A decrease in cerebral blood flow to zero causes death of brain tissue within 4 - 10 min
- ❖ Certain conditions like fever; low BP; hyper or hypoglycemia; electrolyte disturbances; MI…. Can fasten the progression of ischemia to infarction
- ❖ If blood flow is restored to ischemic tissue before significant infarction develops, the patient may experience only transient symptoms, and the clinical syndrome is called **a transient ischemic attack (TIA).**
- ❖ Another important concept is the ***ischemic penumbra***, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction.
    - ○ The penumbra can be imaged by perfusion imaging using MRI or CT (see below and (see figure below)
    - ○ The ischemic penumbra will eventually progress to infarction if no change in flow occurs, and hence saving the ischemic penumbra is the goal of revascularization therapies.

- The factors that determine the progression of ischemic penumbra
  - Collateral circulation; systemic BP; duration and extent of occlusion
  - Systemic conditions like fever, electrolytes, MI



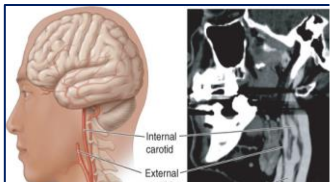
Figure; **Acute left middle cerebral artery (MCA) stroke with right hemiplegia but preserved language.** *B)* Predicted region of infarct (*red*) and penumbra (*green*) based on CT perfusion data. E) CT scan of the brain 2 days later; note infarction in the region predicted in *B* but preservation of the penumbral region by successful revascularization.

Etiologies of ischemic stroke

- Thrombosis
  - Lacunar stroke (small vessel)
  - Large vessel thrombosis
  - Dehydration
- Embolic occlusion
  - Artery-to-artery: Atherosclerosis; Arterial dissection
  - Cardio-embolic: Atrial fibrillation; Mural thrombus; MI; Dilated CMP; MS; IE
- Uncommon causes
  - Hypercoagulable disorders: Protein C deficiency; Protein S def.
  - Antithrombin III deficiency
  - Antiphospholipid syndrome.
  - Vasculopathies: Vasculitis; CADASIL; Fibromuscular dysplasia

Large artery Atherothrombotic Infarctions

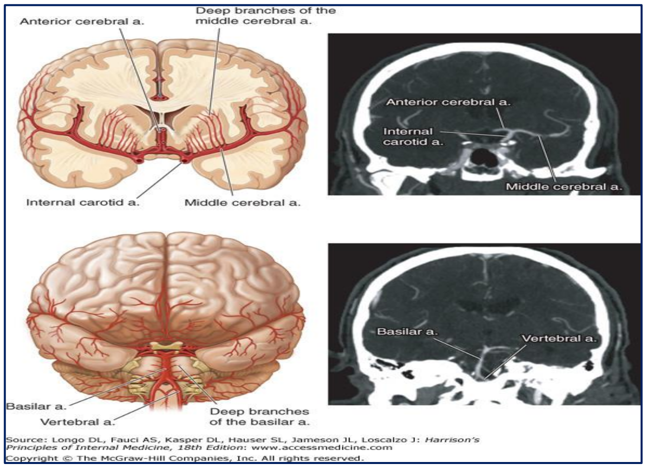
- Almost always occur in patients who already have significant risk factors for cerebro-vascular atherosclerosis: Commonest cause of large artery stroke
- The mechanism of large-artery athero-thrombotic infarction are:
  - Often artery-to-artery embolization.
  - Thrombosis in the pre-existing arterial disease
- Atherosclerosis often affects large vessel commonly:
  - Bifurcation of common carotid artery;
  - proximal ICA;
  - carotid siphon;



- MCA;
- vertebrobasilar arteries

Small vessel or penetrating artery disease

- Small vessel stroke is affection of smaller and penetrating end arteries
- **Atherosclerosis or Lipo-hyalinosis**
- Lacunae usually occur in older patients with long-standing arterial hypertension, current cigarette smoking, and DM.
- The most frequent sites of involvement are the **putamen, basis pontis, thalamus, posterior limb of the internal capsule, and caudate nucleus**.
- About **20-30%** of ischemic stroke


Anterior cerebral a.
Deep branches of the middle cerebral a.
Internal carotid a.
Middle cerebral a.
Anterior cerebral a.
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Cardiogenic embolism

- Cardio-embolic strokes are associated with substantial morbidity and mortality.
- Embolism of cardiac origin accounts for approximately 15% to 20% of all ischemic strokes.
- These cardiac emboli may be composed of platelet, fibrin, platelet-fibrin, calcium, micro-organisms, or neoplastic fragments.
- Common causes are AF; MI; IE; rheumatic MS; Prosthetic valves; CMP; atrial myxoma

Cardio-embolic stroke: AF

- AF if is the commonest cause of cardio-embolic stroke: 2/3rd of cardio-embolic stroke

Table, CHA$_2$DS$_2$-VASc risk stratification score for estimation of stroke risk for nonvalvular atrial fibrillation in adults

CHA$_2$DS$_2$-VASc	Score
1. CHF	1
2. HTN	1
3. Age ☛ ≤ 64 --------------------------- ☛ 65 - 74 ------------------------ ☛ ≥ 75 ---------------------------	 0 1 2
4. DM	1
5. Prior Stroke or TIA or thromboembolism (doubled)	2
6. Vascular disease (MI, PAD, Arterial plaque)	1
7. Sex category ☛ Female ------------------------ ☛ Male ---------------------------	 1 0
Maximum score	10

CHA$_2$DS$_2$-VASc score	Adjusted stroke rate (% per year)	Recommendation
0	0	No antithrombotic
1	1.3	Anti-platelet or anticoagulation
2	2.2	anticoagulation
3	3.2	
4	4.0	
5	6.7	
6	9.8	
7	11.2	
8	10.8	
9	12.2	

CHA$_2$DS$_2$-VASc score Interpretation

- The higher the score, the higher the annual stroke risk.
- For patients with **CHA$_2$DS$_2$-VASc** score >1, anticoagulation is generally indicated unless high bleeding risk/based on HASBLED score/
    - Score 0→ No antithrombotic
    - Score 1→ Anti-platelet or anticoagulation
    - Score ≥ 2 → anticoagulation.
- Commonly used Antiplatelets include Aspirin (1st line) & clopidogrel (2nd line). Commonly used anticoagulants include warfarin, UFH, LMWH

Selected Non atherosclerotic vasculopathies

- Cervico-cephalic arterial dissection
- Traumatic cerebro-vascular disease
- Radiation-induced vasculopathy
- Moyamoya disease
- Fibro-muscular dysplasia
- Vasculitis
- Migraine’s infarction

Cervico-cephalic arterial dissections

- One of the most frequent non-atherosclerotic vasculopathies causing ischemic in stroke in youngs
- Most dissections involve the extra-cranial segment of the internal carotid artery or extra-cranial vertebral arteries.
- Intracranial carotid and vertebro-basilar dissections are less common: Cause ICH/SAH
- Trauma; Fibro-muscular dysplasia; Marfan syndrome; Syphilis…. are common risk factors

Stroke syndromes: Based on the arterial distribution and clinical profile

- TIA (Transient ischemic attacks)
- Large vessel stroke syndromes
    - ✓ Carotid artery system syndromes
        - ☛ MCA syndrome; ACA syndrome
    - ✓ Vertebro-basillar artery syndrome
    - ✓ PCA (Posterior cerebral artery) syndrome
- Small vessel artery (Lacunar) syndrome
- Watershed infarction syndrome

Transient ischemic attacks (TIA)

- A TIA is a transient focal neurologic feature which completely resolve within 24 hours without evidence of infarction on neuro-imaging; attributed to focal vascular even
- **Time based definition**
    - A TIA is a temporary and “non-marching” neurological deficit of sudden onset; attributed to focal ischemia of the brain, retina, or cochlea; and lasting < 24hr’s (i.e. Completely resolve within < 24 hours with normal imaging finding)
    - Yet most TIAs last only a few minutes.
    - Episodes that last longer than 1h are usually due to small infarctions
- **Tissue based definition**
    - Any transient episode, regardless of duration, associated with NO clinically appropriate lesion by neuroimaging be defined as a TIA.
    - Prolonged events (>1—6 hours in duration) be defined as stroke rather than TIA when otherwise clinically appropriate
- The blood flow is restored and the focal deficits improved
- Vasculitis of any cause results both bleeding and infarction

- Vascular disorder — cerebral ischemia — if restored rapidly — TIA
- Vascular disorder — cerebral ischemia — if persisted — infarction — Stroke

TIA: Epidemiology and prognosis

- TIA is a strong predictor of stroke
- One-third of untreated TIA patients having a stroke within 5 years.
- About 1 in 10 patients with TIA experience a stroke in the next 3 months.
- The interval from the last TIA is an important predictor of stroke risk; of all patients who subsequently experience stroke, 21% do so within 1 month and 51% do so within 1 year of the last TIA and 50% of strokes occur within 48 hours of TIA
- Cardiac events are the principal cause of death in patients who have had a TIA.
- 5-6% of annual mortality is by MI

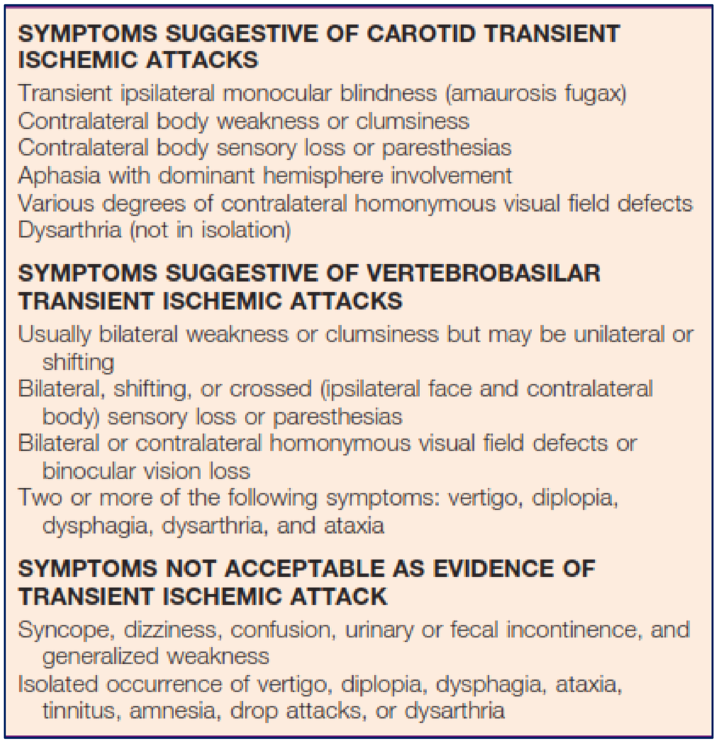
TIA: Etiologies and Risk factors

TIAs may result from:

- Athero-thrombo-embolism that originates from ulcerated extra-cranial arteries
- Emboli of cardiac origin
- Occlusion of small penetrating arteries that arise from the large surface arteries of the circle of Willis
- Altered local blood flow (perfusion failure) due to severe arterial stenosis, non-atherosclerotic vasculopathies, or hyper-coagulable states

TIA: Clinical features

- The onset of TIA symptoms is sudden, reaching maximum intensity almost immediately.
- To qualify as a TIA, therefore, an episode should also be followed by complete clinical recovery.
- The clinical symptoms related with the affected vessel



SYMPTOMS SUGGESTIVE OF CAROTID TRANSIENT ISCHEMIC ATTACKS

Transient ipsilateral monocular blindness (amaurosis fugax)
Contralateral body weakness or clumsiness
Contralateral body sensory loss or paresthesias
Aphasia with dominant hemisphere involvement
Various degrees of contralateral homonymous visual field defects
Dysarthria (not in isolation)

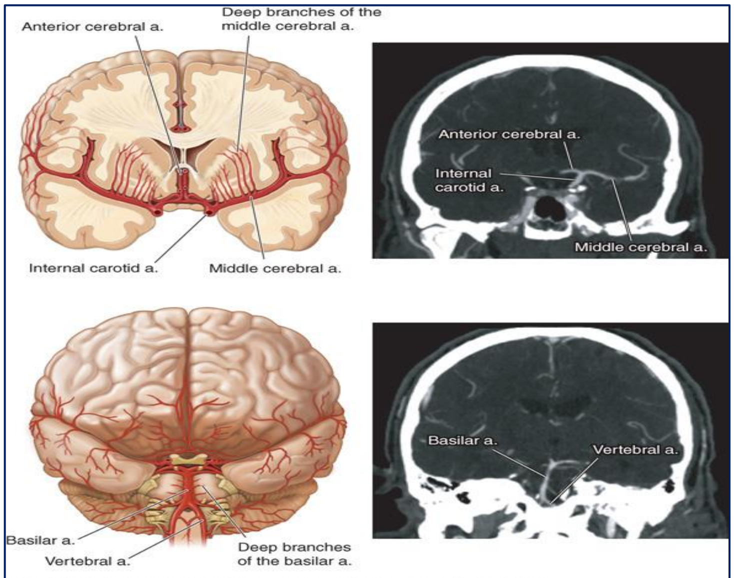
SYMPTOMS SUGGESTIVE OF VERTEBROBASILAR TRANSIENT ISCHEMIC ATTACKS

Usually bilateral weakness or clumsiness but may be unilateral or shifting
Bilateral, shifting, or crossed (ipsilateral face and contralateral body) sensory loss or paresthesias
Bilateral or contralateral homonymous visual field defects or binocular vision loss
Two or more of the following symptoms: vertigo, diplopia, dysphagia, dysarthria, and ataxia

SYMPTOMS NOT ACCEPTABLE AS EVIDENCE OF TRANSIENT ISCHEMIC ATTACK

Syncope, dizziness, confusion, urinary or fecal incontinence, and generalized weakness
Isolated occurrence of vertigo, diplopia, dysphagia, ataxia, tinnitus, amnesia, drop attacks, or dysarthria

Lacunar infarct syndromes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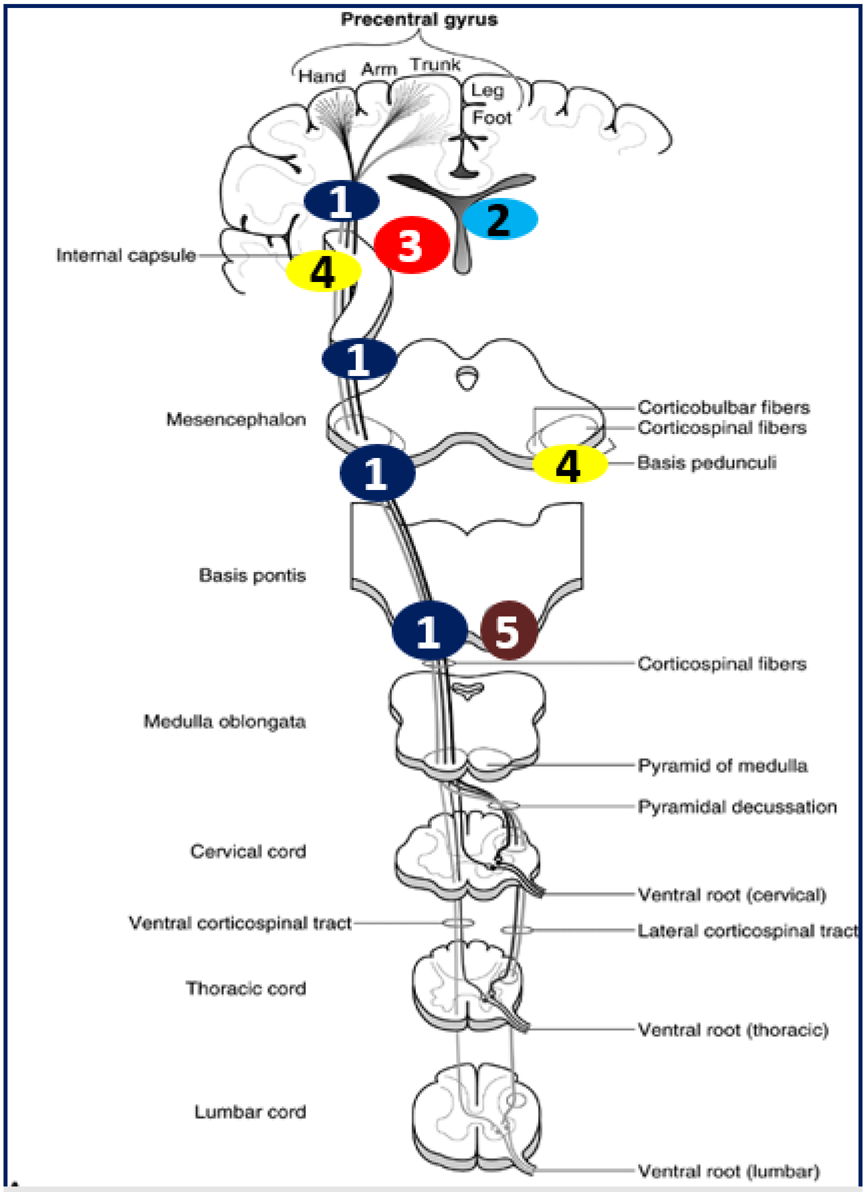
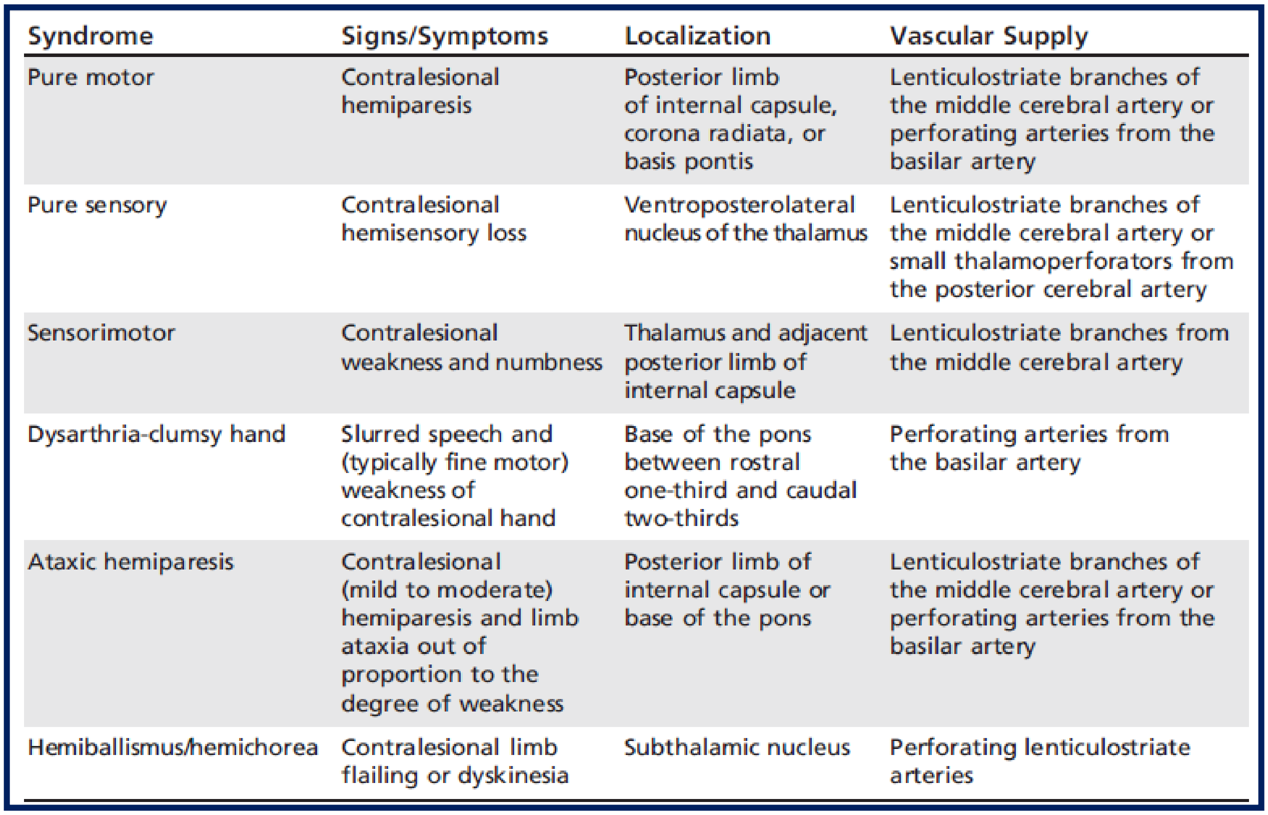
- Ischemic strokes resulting from small-vessel or penetrating artery disease have: Unique clinical, radiological, and pathological features.
- Lacunar infarcts are small ischemic infarctions in the deep regions of the brain or brainstem
- The most common risk factors are Age; DM; HTN and smoking

- These infarctions result from occlusion of the penetrating arteries branches from: The anterior choroidal, middle cerebral, posterior cerebral, and basilar arteries.
- Pathologic changes include Lipohyalinotic changes; microemboli or atherosclerosis.


Precentral gyrus
Hand
Arm
Trunk
Leg
Foot
1
2
3
4
Internal capsule
1
Mesencephalon
Corticobulbar fibers
Corticospinal fibers
1
4
Basis pedunculi
Basis pontis
1
5
Corticospinal fibers
Medulla oblongata
Pyramid of medulla
Pyramidal decussation
Cervical cord
Ventral root (cervical)
Ventral corticospinal tract
Lateral corticospinal tract
Thoracic cord
Ventral root (thoracic)
Lumbar cord
Ventral root (lumbar)

1) **Pure motor hemiparesis**: internal capsule; basis pontis; corona radiata; cerebral peduncle
2) **Pure sensory stroke**: thalamus
3) **Sensori-motor stroke**: internal capsule and thalamus
4) **Homo-lateral ataxia and crural paresis (ataxic hemiparesis):** basis pontis or posterior limb of internal capsule; cerebral peduncle
5) **Dysarthria - clumsy hand syndrome:** Basis pontis

Small Vessel Stroke Syndromes



Syndrome	Signs/Symptoms	Localization	Vascular Supply
Pure motor	Contralesional hemiparesis	Posterior limb of internal capsule, corona radiata, or basis pontis	Lenticulostriate branches of the middle cerebral artery or perforating arteries from the basilar artery
Pure sensory	Contralesional hemisensory loss	Ventroposterolateral nucleus of the thalamus	Lenticulostriate branches of the middle cerebral artery or small thalamoperforators from the posterior cerebral artery
Sensorimotor	Contralesional weakness and numbness	Thalamus and adjacent posterior limb of internal capsule	Lenticulostriate branches from the middle cerebral artery
Dysarthria-clumsy hand	Slurred speech and (typically fine motor) weakness of contralesional hand	Base of the pons between rostral one-third and caudal two-thirds	Perforating arteries from the basilar artery
Ataxic hemiparesis	Contralesional (mild to moderate) hemiparesis and limb ataxia out of proportion to the degree of weakness	Posterior limb of internal capsule or base of the pons	Lenticulostriate branches of the middle cerebral artery or perforating arteries from the basilar artery
Hemiballismus/hemichorea	Contralesional limb flailing or dyskinesia	Subthalamic nucleus	Perforating lenticulostriate arteries

Watershed infarction syndromes

Watershed Ischemia and Infarction

- Occur in the border zone between adjacent arterial perfusion beds of the major circulations:
  - During or after cardiac surgery
  - After an episode of sustained and severe arterial hypotension that can happen after cardiac arrest, prolonged hypoxemia, or bilateral severe carotid artery disease
- May be caused by micro-embolism or hyper-viscosity states.
- Often bilateral but can be unilateral if there is severe arterial stenosis on one side only
- Ischemia in the border zone or junctional territory of the ACA, MCA, and PCA may result in bilateral parieto-occipital infarcts.
- There can be a variety of visual manifestations, including bilateral lower altitudinal-field defects, optic ataxia, cortical blindness, and difficulty in judging size, distance, and movement.
- Ischemia between the territories of the ACA and MCA bilaterally may result in bilateral fronto-parietal infarctions:
- Bi-brachial cortical sensori-motor impairment (“person in a barrel”) and impaired saccadic eye movements
- Ischemia in the border zone between the MCA and PCA may cause bilateral parieto-temporal infarctions.

- Defects such as dyslexia, dyscalculia, dysgraphia, and memory defects for verbal and nonverbal material may be seen

6.2 Hemorrhagic stroke (Intracranial hemorrhage)

- Intracranial hemorrhage consists of various spectrum of bleeding in the cranial fossa and grossly divided into:
    - Traumatic intracranial bleeding
    - Non-traumatic intracranial bleeding
- Based on the location of bleeding:
    - **Intra-cerebral hemorrhage (ICH)**
    - Subarachnoid hemorrhage (SAH)
    - Epidural and subdural hematoma (EDH & SDH)
    - Intra-ventricular hemorrhage (IVH)

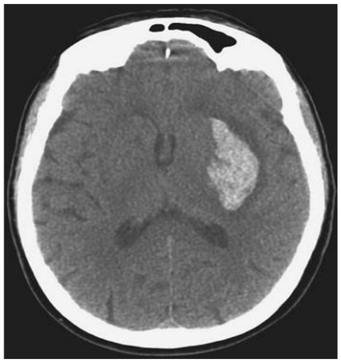
- Intra-cerebral hemorrhage (ICH) is a common neurologic event with significant morbidity and mortality.
- ICH accounts for approximately 10% to 15% of new strokes that occur every year. These numbers are expected to increase with the increased longevity of the population
- The overall morbidity and mortality of ICH has not significantly declined over the past several decades.
- Thirty-day mortality ranges between 30% and 50% and only about 20% will regain independence at 6 months.
- Despite these statistics, most patients have survivable hemorrhages with aggressive medical care

Changing in Epidemiology

- Traditionally, **chronic hypertension** accounted for approximately 80% to 90% of documented ICHs
- More recent epidemiologic studies report that chronic hypertension now accounts for only about half (50%) of all ICHs.
- This change in etiologies largely has to do with improved control of hypertension, the aging of the population, and increased use of anticoagulation.
- Improvements in radiologic techniques also have led to detection of smaller and more subtle hemorrhages
- **In the developing countries: HTN is still the most common and significant cause of ICH**

Hypertensive hemorrhage:

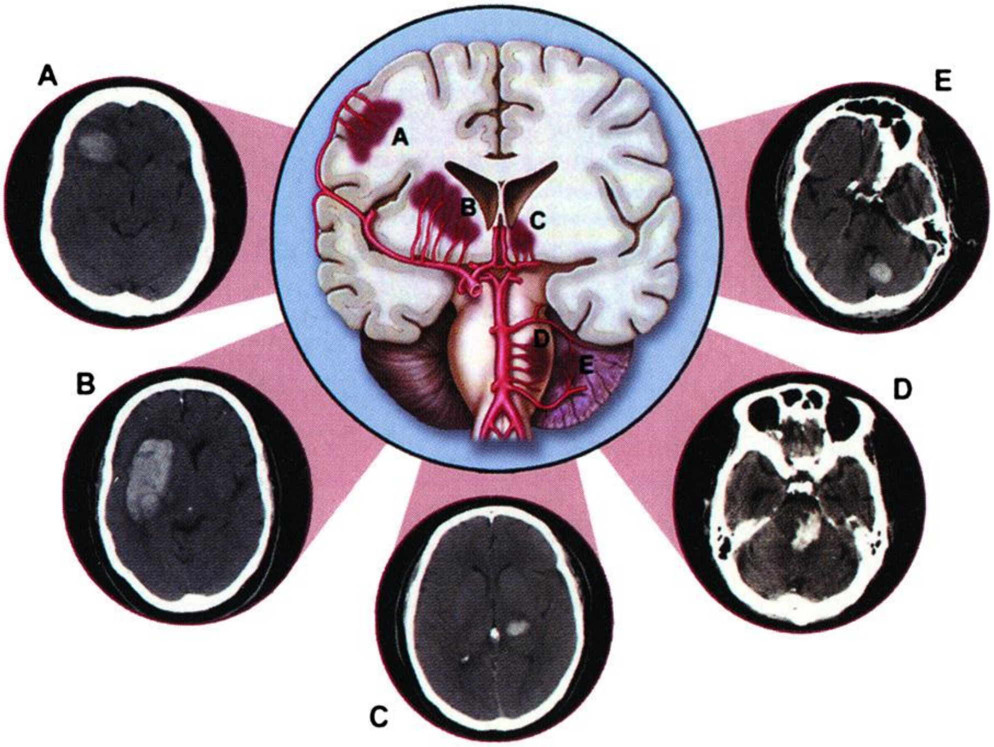
- Bleeding is on deep penetrating arteries: deep brain tissue bleeding



Figure; Hypertensive hemorrhage. Trans axial non-contrast CT scan through the region of the basal ganglia reveals a hematoma involving the left putamen in a patient with rapidly progressive onset of right hemiparesis.

Non hypertensive hemorrhage:

- Bleeding occurs anywhere in the brain depending on the cause: Often lobar and multiple hemorrhage



Etiologies of ICH: Non-Traumatic causes

- Hypertension
- Vascular malformations
- Intracranial tumors
- Bleeding Disorders, Anticoagulants, and Fibrinolytic Treatment
- Cerebral Amyloid Angiopathy
- Granulomatous Angiitis of the CNS and Other Vasculitides

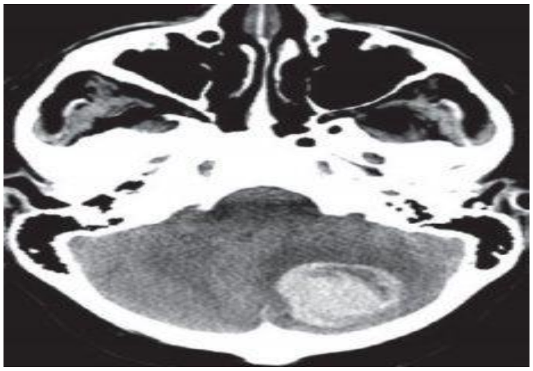
- Sympathomimetic Agents
- Hemorrhagic Infarction

Hypertensive ICH

- **The main cause of ICH is hypertension.**
- The primary role of HTN in ICH is supported by a high frequency (72% - 81%) of hx of HTN, significantly higher BP measurements at admission in comparison with patients with other stroke subtypes, high frequency of LVH, and over-representation of common genetic variants associated with hypertension.
- Excluding patients with hemorrhage associated with ruptured AVMs, tumor, anticoagulant and thrombolytic therapy, and cocaine ingestion; it was determined that the cause was hypertension in 72% of patients. Although the prevalence of HTN in ICH cases is dropping to 50% in recent years
- Patients with severe acute hypertension may have a similar risk as those patients with chronic low-grade hypertension: the issue is **uncontrolled HTN**
- The vascular lesion produced by chronic hypertension that leads to arterial rupture and ICH is probably lipohyalinosis of small intra-parenchymal arteries: Ultimately formation of micro aneurysm
- The **most related risk factors** for development of theses vascular changes with HTN are **duration** of HTN and **older age.**
- Common sites of bleeding are: Putamen > Lobar > Thalamus > Cerebellum > Pons……

Bleeding into a tumor

- Relatively rare (<10% of ICH cases).
- The tumor types most likely to lead to this rare complication are **Glioblastoma multiforme** or **metastases from melanoma, bronchogenic carcinoma, choriocarcinoma**, or **renal cell carcinoma**
- Different from HTN related ICH:
- Papilledema at presentation and headache long before bleeding
- Location of bleeding: Corpus callosum, Multiple bleeds
- CT signs of ring forming bleed; nodular enhancement and huge surrounding edema

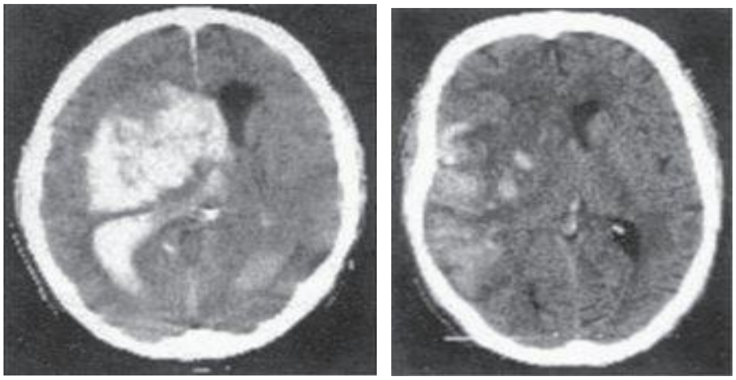


Use of anticoagulation

- Patients on long-term anti-coagulation have a risk of ICH of approximately 1% per year, although the highest risk is within the first year.
- Risk factors include:
  - ✓ Older age
  - ✓ Hypertension
  - ✓ Previous ischemic stroke, and leukoariosis.
- ICH risk is significantly increased when the INR is > 3.5 and add on use of anti-platelets.

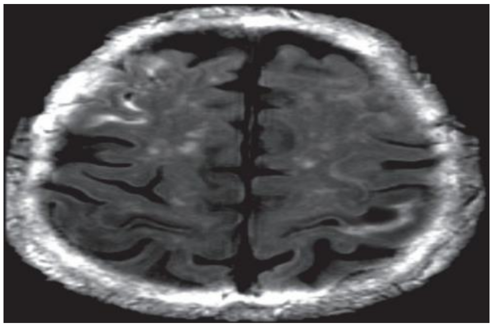
Signs of micro-bleeds in imaging

- These hemorrhages have certain distinctive clinical characteristics when compared to HTN induced ICH:
- They tend to present with a slowly progressive course, at times over periods as long as 48 to 72 hours.
- The bleeding expands with relatively larger size before clinical features: Often multiple Bleeding from other areas



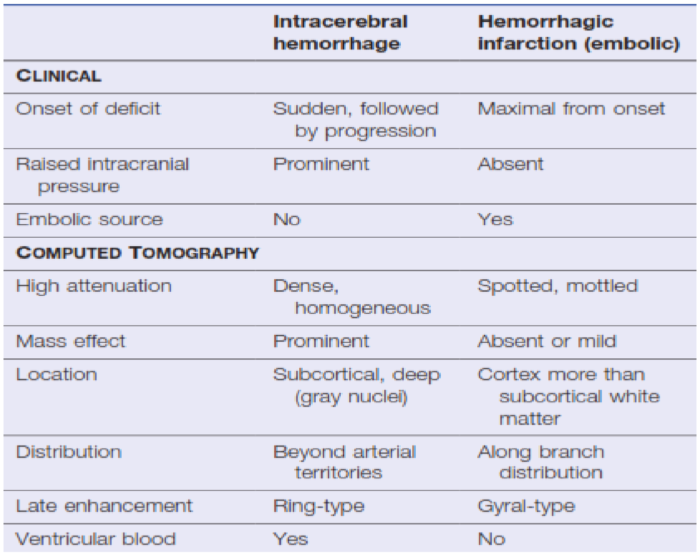
Cerebral amyloid angiopathy (CAA)

- CAA is characterized by selective deposition of ß-amyloid in the walls of cerebral vessels, primarily small and medium sized arteries of the cortex and leptomeninges.
- CAA increases steadily with age, reaching 60% in individuals > 90 years.
- It characteristically causes ICH in the elderly and is rarely documented before the age of 55 years
- The superficial location of the affected vessels in the cortex and leptomeninges is responsible for a predominantly lobar location of ICH.
- Multiple and recurrent lobar bleeding
- 30% of cases have dementia: ADs
- Focal deficits or seizure may occur before major bleeding



Difference between ICH and Hemorrhagic infarction

- Hemorrhagic infarction characteristically occurs
    - ✓ In the setting of **cerebral embolism**
    - ✓ Rarely following restoration of cerebral perfusion to border zone infarcts that had resulted from global hypo-perfusion
    - ✓ Following cerebral venous thrombosis



	Intracerebral hemorrhage	Hemorrhagic infarction (embolic)
CLINICAL		
Onset of deficit	Sudden, followed by progression	Maximal from onset
Raised intracranial pressure	Prominent	Absent
Embolic source	No	Yes
COMPUTED TOMOGRAPHY		
High attenuation	Dense, homogeneous	Spotted, mottled
Mass effect	Prominent	Absent or mild
Location	Subcortical, deep (gray nuclei)	Cortex more than subcortical white matter
Distribution	Beyond arterial territories	Along branch distribution
Late enhancement	Ring-type	Gyral-type
Ventricular blood	Yes	No

Pathophysiology of hematoma formation

- ✓ The exact means by which ICH occurs is not completely understood: The mechanism of ICH depends on the cause of bleeding
- ✓ ICH secondary to hypertension occurs in areas of the brain that are perfused by the lenticulo-striate arteries arising directly from the large basal cerebral arteries.

SUSEPTIBLE VESSEL

These vessels are branched from large arteries proximal to arterioles where cerebral auto -regulation occurs

CHRONIC INJURY

Atherosclerosis and HTN will result a series of injuries to these vessels ultimately result in thickening and fragile

ICH

The exact mechanism how these vessels bleed is not known but:

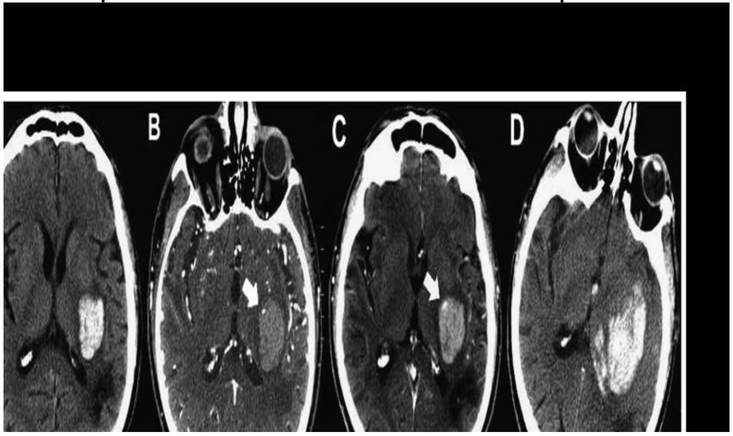
Micro anurysm formation; sudden high BP and inability for the vessels to maintain RBCs in the vessels

Pathophysiology of hematoma expansion

- CT studies reveal that approximately 40% of ICHs will expand from the initial size of the hemorrhage.
- In those patients in whom hematoma expansion is detected, 75% will have hematoma expansion within the first 6 hours, and almost all of the rest will have expansion within 24 hours
- How expansion occurs is similarly unknown.
- Traditionally, hemorrhages were believed to expand because of local mass effect leading to progressive tearing of small vessels and damage of neurologic tissue.
- It is now believed that much of the hemorrhage expands along white matter tissue planes that surround intact neurologic tissue

Factors related with hematoma expansion

- Poorly controlled DM and SBP > 200 mm Hg
- The role of anti-platelet use and hematoma expansion is unclear
- The finding of contrast extra-vasation during CTA has been used to identify patients at risk for hematoma expansion: **SPOT SIGN**



Secondary brain injury after bleeding

- If and how secondary damage occurs is also a matter of debate.

1. MRI volumetric analysis reveals a decrease in hemispheric volume ipsilateral to an ICH: **Compression effect**.
2. Similarly, apoptotic markers are increased in patients with ICH, suggesting that much of ICH-related damage may be secondary: **Apoptosis induced.**
3. Red blood cell lysis occurs approximately 6 to 8 days after the initial hemorrhage: **Complement induced inflammation.**
4. A subsequent release of hemoglobin and its byproducts (primarily thrombin) is believed to be involved in both direct and indirect neural toxicity: **Free Iron toxicity**
5. **Damage to the BBB** result in brain edema and subsequent complications.

Clinical presentation

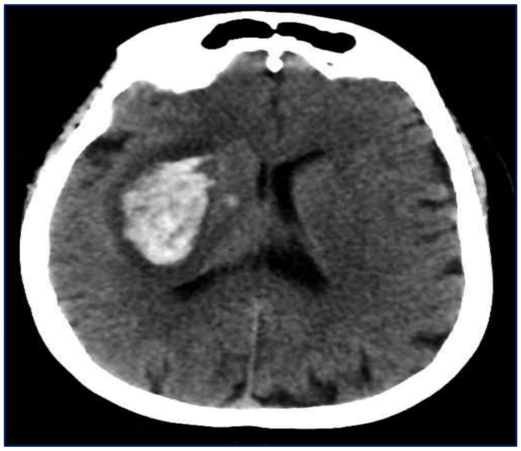
- The clinical presentation of ICH has two main elements:

1. Symptoms that reflect the effects of intracranial hypertension
2. Those smx's that are specific for the location of the hematoma

- A characteristic of ICH at presentation is the frequent progression of focal neurological deficits over periods of hours.
- This early course reflects progressive enlargement of the hematoma
- The general clinical manifestations of ICH related to increased ICP (headache, vomiting, and depressed level of consciousness) vary in their frequency at onset of ICH.
- The correlation of these symptoms (especially abnormal level of consciousness) with hematoma size applies to all anatomical varieties of ICH, which in turn relates directly to mortality.

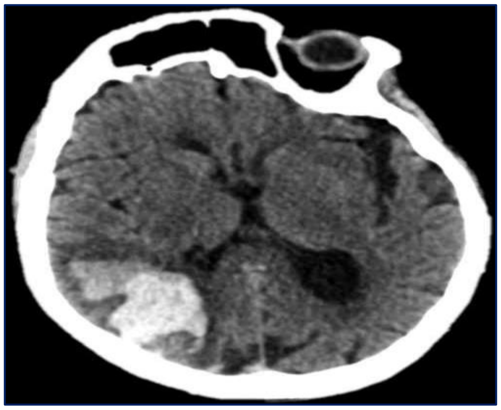
Putaminal hemorrhage

- The most common variety of ICH, 35% of cases.
- Dense hemiplegia; dysarthria; contra-lateral gaze palsy and progress to coma.
- Commonest cause is HTN
- Ventricular extension seen as a poor prognostic factor with higher mortality



Lobar hemorrhage

- Lobar hemorrhage is second to putaminal hemorrhage in frequency, 25% of ICH cases.
- Non-hypertensive mechanisms including AVMs, sympathomimetic agents (in young patients), and CAA (in elderly patients) are frequent causes.
- The peripheral location of these hematomas explains the lower frequency of coma at onset.
- Seizure occurs in many cases



6.3. Management of Stroke

Evaluation of Acute Stroke

- Time is Brain: Early fibrinolytic treatment
  - ✓ *"Be quick, but don't hurry."*
  - ✓ Time took from initial evaluation to door of CT scan should not exceed 30 minutes
- The main goals of evaluation of acute stroke is:
  1. To diagnosis of acute stroke or other stroke mimics

2. To differentiate ischemic from hemorrhagic stroke and analyze the subtype of stroke
3. Identify prompt risk factors
4. Assess the severity of the disease and indications of rTPA

- ➢ The most important and initial evaluation was the onset of the symptoms with the exact clock: Example 2:00 AM rather than using hours or minutes like 2 hours ago.
- ➢ The mode of onset and chronology of symptoms: helps to identify stroke syndromes

Management principles

1. Differentiate Ischemic from hemorrhagic stroke ASAP (Clinically, Emergency CT in best setups)
2. ABC of life
    - ✓ Treat and prevent aspiration (target is saturation ≥ 94%)
    - ✓ Treat hypotension and shock (may be cause of stroke)
3. RBS → if low manage as hypoglycemia
4. Emergency CT
    - ✓ Non contrast CT
    - ✓ Can detect ischemia as early as 1hr and hemorrhage within 10 min (i.e used to r/o hemorrhagic stroke)
    - ✓ If there is no abnormality in CT, treat as ischemic stroke

    N.B MRI is very sensitive and specific, but it needs time for Dx
5. Identify the cause
6. Specific and supportive management based on type of stroke

A. Management of ischemic stroke

Let's show you **order sheet example for Ischemic stroke in our set up** before going to detailed management principles → it may be different based on your patient comorbid conditions and complications.

12/09/2013 E.C 8:30 DLT	Treatment
	New order
	❖ Secure double IV line
	❖ Put on 100% O_2 (if SPO_2 is < 95%). E.g. Put on 1L/min of INO_2
	❖ NG Tube feeding with 300ml of semisolid food every 3 hours and Monitor swallow test daily (this order is, if swallow test is -ve)
	❖ Follow Vital sign strictly
	❖ Catheterize and follow input and output strictly (i.e. Maintain fluid balance)
	❖ Do RBS QID (control of glucose to be between 140 mg/dL and 180 mg/dL)
	❖ Position every 1hr (for critical pt) or every 2hr (for noncritical pt)
	❖ Omeprazole, 20mg, PO/via NG tube, BID
	❖ UFH, 5,000 IU, Sc, BID (Consider Warfarin if there is CHADVASC score indication)
	❖ Aspirin, 325 mg, PO, Loading then 81mg (81-100 mg), PO, daily

12/09/2013 E.C. 4:00 NLT	❖ Atorvastatin 80 mg daily (for at least 3 months, then 40 mg daily for life long which should be continued with chronic OPD follow up)
	Dr. Mulualem. G (GP)
	Added order
	If BP > 220/110 mmHg ❖ Lasix or HCT Plus ❖ ACE-I (Captopril/enalapril) or CCB (amlodipine)
	If Hyperglycemia (>180 mg/dL) give insulin → see dose below
	If febrile → antipyretics and cooling cloths (cold compression)
	If GCS < 8, insert NG tube and Intubate. Routine NG tube, airway, and catheter care with eye and mouth care.
	If there is DVT and PE ❖ UFH, 5,000 IU, IV, loading then 250 IU/kg/dose, Sc, BID ❖ Add warfarin 2-5mg, PO/IV, on day 1 or 2 of UFH, daily for 2 days, check INR after 2 days and adjust based on the result ❖ Overlap warfarin and UFH for at least 5 days until desired INR/INR=2-3/ maintained for 24hr then discontinue UFH.
	If there is cerebral edema (increased ICP) ❖ Head position between 30 and 45° ❖ Mannitol Loading dose 1g/kg over 30-60min, followed by a maintenance dose of 0.5g/kg every 4-6hrs (if measuring weight is difficult, mannitol 300ml loading over 30 min then a maintenance dose of 100ml QID then deescalate) ❖ Maintenance of euvolemia with NS, avoid dextrose solutions
	Treat causes and comorbidities → Atrial fibrillation, MI, UTI, Pneumonia....
	Treat electrolyte disturbance
	❖ Link to physiotherapy (when patient is stable and before discharge)
	rTPA is not available in most setups of Ethiopia
	For hemorrhagic stroke, all managements above are the same except; avoid UFH, warfarin, aspirin, and atorvastatin. Consider indication for surgical removal. It needs strictly control of BP (see Hemorrhagic stroke mgt below)

- Elements of stroke management
  - ABC of life
  - Treatment of acute ischemic stroke
  - Treatment and prevention of causes and risk factors
  - Comprehensive functional rehabilitation
  - Comprehensive nursing care and prevention of complications

- Three basic principles of Acute stroke care include;
  1. **Acute reperfusion therapy** (Achieve timely re-canalization of the occluded artery and reperfusion of the ischemic tissue)
     1.1 IV thrombolysis with rTPA (recombinant tissue plasminogen activator = Alteplase)
     1.2 mechanical thrombectomy

2. **Optimize collateral flow**
3. **Avoid secondary brain injury**

- ➢ All Should be performed at the same time
- ➢ All are directed for Salvaging ischemic penumbra

1. Acute reperfusion therapy

- There is incontrovertible evidence that IV thrombolysis with rTPA and endovascular thrombectomy with a retrievable stent improve neurologic outcomes in patients with acute ischemic stroke.
- Both treatments should be administered as quickly as possible after stroke onset, can be combined, and are safe in appropriately selected candidates.
- IV thrombolysis and mechanical thrombectomy can produce reperfusion injury after re-canalization.
- Reperfusion injury can manifest with hemorrhage and edema.
    - ✓ It is more severe when the area of established infarction is large
    - ✓ Good patient selection and prompt treatment are crucial to avoid this complication.

1.1 IV Thrombolysis

- ✓ IV thrombolysis with rTPA is proven to be effective in improving functional outcomes after an ischemic stroke **up to 4.5 hours after symptom onset.**
- ✓ The first step of evaluation of acute stroke is to decide eligibility for rTPA.
    - Time of onset
    - Age > 18 yrs
    - RBS; BP
    - NIHSS score and CT findings
    - Other Contraindications

Indication for r-TPA

- Clinical diagnosis of Ischemic stroke
- Onset of symptoms to time of drug administration ≤4.5 h; Best in the first 3 hours
- CT scan showing no hemorrhage or edema of >1/3 of the MCA territory
- Age 18 ≥ years

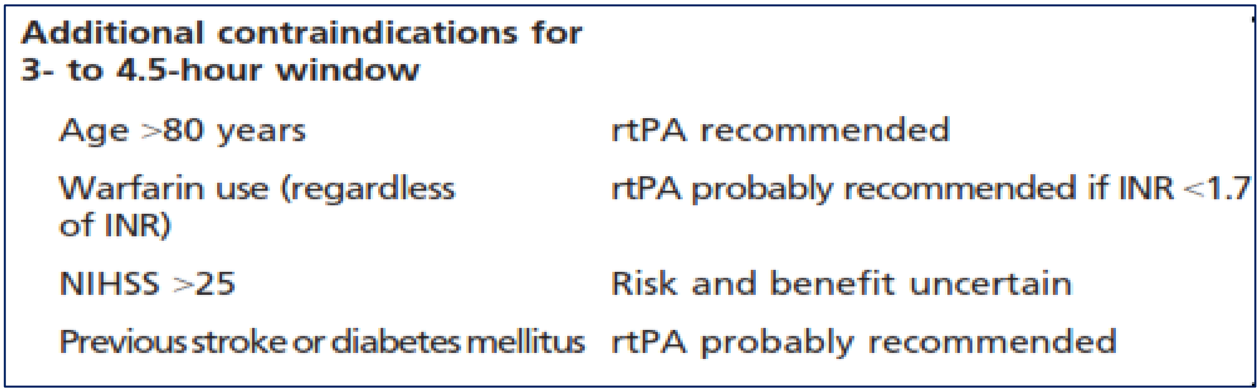
ABSOLUTE CONTRAINDICATIONS

- Sustained BP >185/110 mmHg despite treatment
- RBS < 50 mg/dl or > 400 mg/dl
- Bleeding diathesis; INR > 1.7, on anticoagulants or Platelets < 100,000/mm;
- Recent head injury or intracerebral hemorrhage; History of head injury in the last 3 months
- Major surgery in preceding 14 days
- GI bleeding in preceding 21 days
- Recent myocardial infarction
- Arterial puncture at non-compressible site within 7days;
- Previous ICH recently or suspected SAH; brain tumor; AVM

- BP > 185/110;

OTHER CONSIDERATIONS

- Minor stroke (Typically NIHSS score <5) and rapidly improving deficits
- Pregnancy
- Seizure at onset with post-ictal residual deficits
- Major extra cranial injuries and surgery in the last 15 days



Additional contraindications for 3- to 4.5-hour window

Age >80 years	rtPA recommended
Warfarin use (regardless of INR)	rtPA probably recommended if INR <1.7
NIHSS >25	Risk and benefit uncertain
Previous stroke or diabetes mellitus	rtPA probably recommended

Administration of rtPA

- IV access with two peripheral IV lines (avoid arterial or central line placement)
- Review eligibility for rtPA
- Administer **0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 hour**
- Frequent cuff blood pressure monitoring
- No other antithrombotic treatment for 24 h
- For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently
- Avoid urethral catheterization for ≥2 h

CXN of rTPA

- Oro-lingual angio-edema
  - ✓ is a rare but potentially serious complication of rtPA administration: especially in those with ACE-I:
  - ✓ Rx with anti-histamines and steroids
- ICH: 1.9 % - 6.4%.
  - ✓ Treatment includes;
    - Control of hypertension (systolic target 140 mmHg to 160 mm Hg)
    - Reversal of the fibrinolytic effect with cryoprecipitate (10 units) or an antifibrinolytic agent (tranexamic acid 10 mg/kg to 15 mg/kg IV over 20 minutes or ε-aminocaproic acid 5 g IV followed by an infusion of 1 g/h if necessary

1.2 Mechanical thrombectomy

Clinical indications

- Age ≥ 18 years
- NIHSS score ≥ 6
- Time from Symptom onset to groin puncture < 6 hours
- Good prestrike functional status
- Presence of proximal intracranial artery occlusion
- ASPECTS score ≥ 6 on baseline CT scan (ASPECTS = Alberta stroke program early CT score)

Other indications for mechanical thrombectomy

- ✓ Failed rTPA
- ✓ Large thrombus on imaging

Standard Post reperfusion care

- ➢ Admission to a step-down or ICU
- ➢ Maintenance of NPO status until dysphagia screening is performed to avoid aspiration pneumonia
- ➢ Administration of isotonic IV fluids (not dextrose containing because of risk of hyperglycaemia)
- ➢ BP and neurologic monitoring every 15 minutes for 2 hours, then every 30 minutes for 6 hours, then every hour for 16 hours after treatment
- ➢ Aggressive blood pressure treatment if SBP is > 180 mm Hg or DBP is >105 mm Hg
- ➢ **Emergent CT scan** of the brain if neurologic decline, acute increase in blood pressure, nausea, vomiting, or new headache is present to **rule out haemorrhagic transformation**
- ➢ Repeat brain imaging at 24 hours to assess for asymptomatic haemorrhage and to allow initiation of anti-platelet therapy

2. Optimize collateral circulation

- ➢ **BP** and Stroke
  - ✓ Higher BP at the onset of stroke is required; part of physiologic response to perfuse collateral vessels
  - ✓ BP should be lowered if above 220/110 mmHg if rTPA is not used; reduce by 15% in the first 24 hours: if rTPA to be used keep the BP below 180/90.
  - ✓ Diuretics and ACE-I are preferred but any treatment choice
  - ✓ BP should be improved if its low; Using IV fluids and vasopressors

- ➢ **Hyperglycemia / hypoglycemia**

  - ✓ Hyperglycemia (>180 mg/dL) and Hypoglycemia during the first 24 hours after stroke are poor prognostic indicator.

- ✓ Keep RBS level between 70 and 180 mg/dl in the acute setting: Dextrose/insulin
- ✓ If there is hyperglycemia give insulin with sliding scale principle*

RBS value (mg/dl)	Insulin dose (IU) to be given
181 — 200	2
201 — 250	3
251 — 300	4
301 — 350	5
351- 400	6
> 400 ✓ Check Urine ketone and glucose ✓ Consider DKA if S/he has DM	

i.e. increase by 1 IU for every rise of 50 mg/dl

* Look at DM management for more

3. Prevent secondary brain injury

- ❖ Conditions that exacerbate neurologic injury and ischemic penumbra include:
    - ✓ Fever and dehydration
    - ✓ Aspiration and nutritional deficiency
    - ✓ Airway obstruction and hypoxia
    - ✓ Electrolyte disturbances and organ dysfunction
    - ✓ Presence of complications including: infections, DVT, cerebral edema, **Neuro-protective treatments**: Hypothermia; Fluoxetine

3.1 Airway protection and oxygenation

- ✓ Stroke patient should be positioned appropriately: flat or 30° up depending on the condition of the patient
- ✓ Oral secretions should be removed; oral airway if necessary; intubation if GCS < 8
- ✓ Saturation of oxygen should be above 95% in acute state; if low assess airway and reasons for lower oxygenation and put on them with 100% oxygen.
- ✓ Assess the respiratory pattern and rate and assess sign of aspiration

3.2 Nutrition and Feeding

- ➢ Assess for dysphagia; and aspiration using swallow test and GCS
- ➢ NG tube feeding and intravenous fluid in early states of stroke
- ❖ NG tube for
    - ✓ Feeding
    - ✓ Prevention of aspiration
    - ✓ Dysphagia

N.B

- Oral or oropharyngeal dysphagia is common Because of CN palsy (pseudo bulbar palsy)
- Check **swallow test**
    - Give **30ml of water** to swallow with one breath
    - S/he should complete with in 10 sec
    - If there is **chocking episode and remnant in mouth** swallow test is -ve → insert NG tube for feeding. If not, swallow test is +ve and s/he can take PO
    - Absent gag reflex doesn't mean -ve swallow test
- Feeding in NG tube
    - Calculate metabolic demand (md)
    - Metabolic demand of adult is 2000 - 2500 ml per day
    - md coefficient = md x 1.5
    - Divide the total amount of metabolic demand for 8 to give over 3hr. e.g. if the md is 2400ml, then 2400/8 = 300ml, so give 300ml every 3hr (the trend in our setup is, NG Tube feeding 300ml every 3hr)
    - add insensible loss
    - The food for feeding should be semisolid
    - If there is concomitant DM, avoid high sugar containing food

3.3 Fever, electrolyte and organ function

- Assess for fever; if occurred assess for site of infection and treat; use antipyretics and cooling cloths (cold compression) to reduce fever
- Monitor electrolyte frequently and treat: commonest abnormality is hyponatremia
- Monitor LFT and RFT as well as cardiac evaluation frequently and treat

3.4 Standard nursing care

- Bed side care for the clothing and intermittent positioning to prevent pressure sore
- Routine NG tube; airway; and catheter care with eye and mouth care
- Monitor swallow daily and act accordingly

3.5 Treatment of stroke complications

3.5.1 Infections

- Fever after a stroke should prompt evaluation for common sources, including pneumonia and UTI.
- **Pneumonia is the commonest cause of fever** in the first 48 hours of stroke with risk factors including aspiration; atelectasis; intubation…

- Early mobilization, airway care and dysphagia assessment prevent pneumonia
- UTI occur in 11% to 15% of patients with stroke, and are often seen during the first 5 days of the hospitalization. Prolonged catheter use and poor catheter care are risk factors

3.5.2 DVT

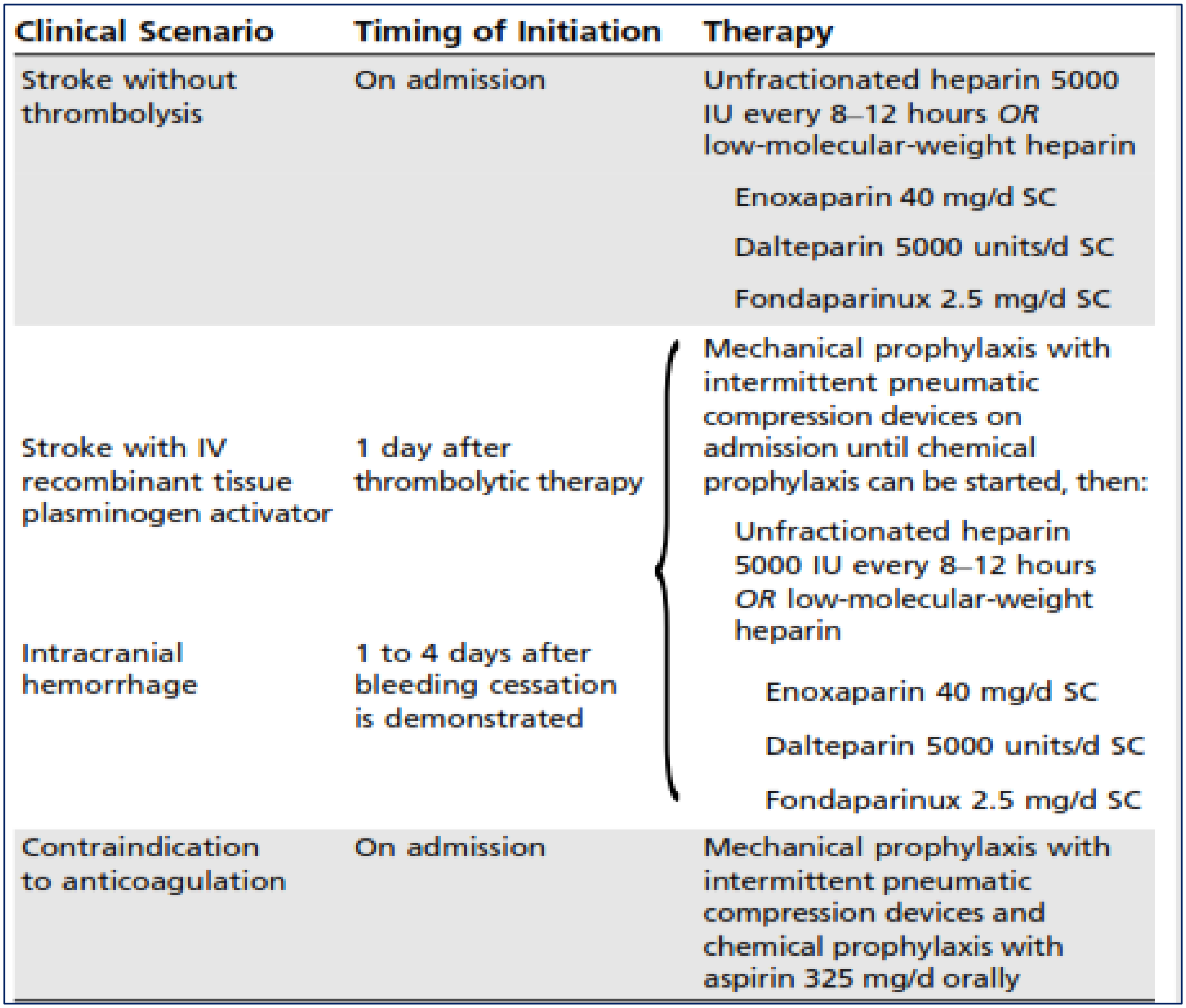
- The development of DVT may take place as early as day 2 after stroke onset, with a peak incidence between days 2 and 7.
- PTE occurs in 1-3% of stroke with mortality rate of 13-25%
- Severe disability; old age and dehydration are risk factors

DVT and PE treatment

- Initiate warfarin 2-5mg, PO/IV, on day 1 or 2 of parenteral anticoagulation therapy (e.g LMWH or UFH)
- Overlap warfarin and parenteral anticoagulant for at least 5 days until desired INR (therapeutic INR = 2-3) maintained for 24hr then discontinue parenteral therapy

N.B

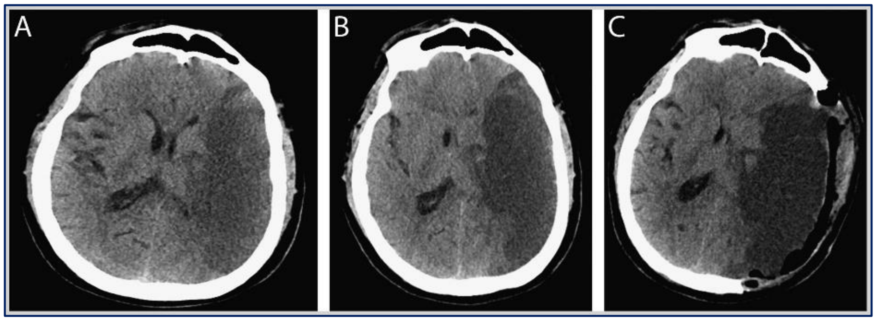
Heparin dose		
	Prophylaxis	Therapeutic
UFH	5,000 IU, Sc, BID	5,000 IU, IV, loading then 250 IU/kg/dose, sc, BID or 80 IU/kg/hr maintenance dose
LMWH (e.g. enoxaparin)	1mg/kg/day (40mg, sc, daily)	1mg/kg/dose, sc, BID



Clinical Scenario	Timing of Initiation	Therapy
Stroke without thrombolysis	On admission	Unfractionated heparin 5000 IU every 8–12 hours *OR* low-molecular-weight heparin Enoxaparin 40 mg/d SC Dalteparin 5000 units/d SC Fondaparinux 2.5 mg/d SC
Stroke with IV recombinant tissue plasminogen activator	1 day after thrombolytic therapy	Mechanical prophylaxis with intermittent pneumatic compression devices on admission until chemical prophylaxis can be started, then: Unfractionated heparin 5000 IU every 8–12 hours *OR* low-molecular-weight heparin Enoxaparin 40 mg/d SC Dalteparin 5000 units/d SC Fondaparinux 2.5 mg/d SC
Intracranial hemorrhage	1 to 4 days after bleeding cessation is demonstrated	
Contraindication to anticoagulation	On admission	Mechanical prophylaxis with intermittent pneumatic compression devices and chemical prophylaxis with aspirin 325 mg/d orally

3.5.3 Cerebral edema

- Neurologic deterioration is often observed within 72 to 96 hours from onset of the stroke.
- **Decreased level of arousal** may be the **earliest clinical change** indicating symptomatic cerebral edema.
- Other early signs are: increased sleepiness; headache, N/V; worsening of motor deficit and pupillary signs
- In general, sign and smx of cerebral edema include
    - Decreased alertness
    - Projectile vomiting
    - Cushing triad → HTN, bradycardia, irregular breathing pattern
    - Papilledema
    - Midline shift and surrounding edema on CT scan



- **Treatment** includes:
    - ✓ Head position between 30 and 45°
    - ✓ Start osmotic therapy with Hypertonic saline or IV mannitol
    - ✓ Mechanical ventilation: Hyperventilation
    - ✓ Steroid (like dexamethasone, 6mg, IM) → for meningitis, brain tumor, brain abscess
    - ✓ Consider decompressive surgery
- Patients at the **highest risk for developing malignant cerebral edema** are:
    - ▪ Internal carotid artery or proximal middle cerebral artery with a large infarction volume;
    - ▪ CT with frank hypodensity within 6 hours; more than 1/3rd of hemisphere infarction; midline shift > 5 mm in the first two days of stroke
- Clinical factors associated with cerebral edema:
    - – An NIHSS score > 20 in dominant hemispheric strokes or > 15 in non-dominant hemispheric strokes has been associated with malignant infarction.
    - – Other clinical factors associated with edema are early nausea and vomiting, female sex, congestive heart failure, and leukocytosis at presentation.
- General managements of cerebral edema include
    - ✓ Frequent neurologic examinations to monitor for neurologic deterioration
    - ✓ Maintenance of normothermia
    - ✓ Avoidance of hypercarbia
    - ✓ Maintenance of euvolemia while avoiding hypotonic solutions
    - ✓ Control of glucose to between 140 mg/dL and 180 mg/dL
    - ✓ Correction of hyponatremia
    - ✓ Prevention of aggravating factors

Management of increased ICP in the setting of acute ischemic stroke

Correction of factors exacerbating increased ICP

- ➢ Hypercarbia
- ➢ Hypoxia
- ➢ Hyperthermia
- ➢ Acidosis

- Hypotension
- Hypovolemia

Positional

- Initial management of elevated ICP includes elevating the head of the bed to 30 degrees (avoidance of flat supine position) and appropriate sedation and pain control.
- Avoidance of head and neck positions compressing jugular veins

Medical management

- Endotracheal intubation and mechanical ventilation if GCS < 8
- Hyperventilation to a Pco_2 of 35 ± 3 mmHg (if herniating)
- **Mannitol**
  - ✓ **Loading dose 1g/kg/dose over 30-60min**, followed by a **maintenance dose of 0.25 to 5 g/kg/dose (usually 0.5g/kg) TID or QID** (depending on clinical status, serum osmolality, volume status and ICP measurement)
    - It should not be given over a long period (as continuous infusion)
    - **20g of mannitol = 100ml (i.e. mannitol 20g/100ml, 1g=5ml)** (for e.g. for 60kg adult pt loading dose 1g x 60kg = 60g = 300ml, maintenance 0.5g x 60kg =30g = 150ml)
    - **The usual trend in our setup is 300ml loading over 30 min then a maintenance dose of 100ml QID then deescalate → 50ml, 25ml…**
    - Inspect for crystals prior to administration. If crystals are present, re dissolve by warming solution
  - ✓ The goal is dehydrating the brain not the patient and maintenance of serum osmolality 300-320mOsm/L.
- Consider **hypertonic saline** (23.4%)
  - ✓ Loading dose 30ml over 10-20min followed by maintenance dose of 3% hypertonic saline, 1ml/kg/hr titrated to a serum sodium of 150-155meq/l

Fluid management

- Maintenance of euvolemia with Isotonic solution **using NS**
- **Avoidance of glucose containing** solutions because hyperglycemia is associated with worse prognosis for stroke
- Replacement of urinary losses with NS in patients receiving mannitol.

4. Management of risk factors and prevention of recurrent stroke

GENERAL MEASURES

- Control of associated risk factors such as hypertension, dyslipidemia, cigarette smoking and alcohol intake; dietary treatment and exercise
- General measures include
  - Anti-thrombotic agents
  - Modifying risk factors

  - Antihypertensive agents
  - Statin treatment
  - Diet and physical activity
- The prevention strategy depends on the mechanism of Ischemic stroke

4.1 Platelet anti-aggregates

- Platelet anti-aggregates: include **Aspirin**; **Clopidogrel** and **Ticlopidine** as well as Phospho-di esterase inhibitors like **Dipyridamole.**
- first line of therapy in patients at high risk for stroke

Aspirin

- ✓ **Loading dose of 325 mg then 81**-100 **mg maintenance** should be given as early as possible and ideally within 48 hours of stroke onset.
    - Alternative: Clopidogrel 75 mg Po daily

4.2 Anticoagulants and statins

Lipid lowering agents

- ✓ **High dose statins;**
  - **Atorvastatin (80 mg)** for at least 3 months, then half the dose (40 mg) for life is recommended in arterial causes of stroke
    - *Age ≤75 years:* High-intensity therapy: 80 mg once daily; if unable to tolerate, may reduce dose to 40 mg once daily
    - *Age >75 years or not a candidate for high intensity therapy:* Moderate-intensity therapy: 10 to 20 mg once daily
    - For *Type 1 or 2 diabetes and age 40 to 75 years:* Moderate-intensity therapy: 10 to 20 mg once daily
  - Alternative: Rosuvastatin 40 mg Po daily

Warfarin

- ✓ Inhibits the synthesis of factors II, VII, IX, and X, as well as proteins C and S: follow up with PT; PTT and INR
- ✓ Indicated for primary and secondary prevention of stroke in patients with NVAF: **depends on CHA_2DS_2Vas score**
- ✓ Other Indication for secondary prevention includes: cardio-embolic stroke following structural diseases of the heart like RHD; MI; DCMP…. Or following large vessel stroke with AF.
- ✓ **Initial dose; 2-5mg, PO/IV, daily for 2 days, check INR after 2days and adjust based on the result**

N.B

Indication for dual anticoagulant

- ➢ Recurrent Stroke

- Resistance to Single anticoagulant
- Intracranial atherosclerosis
- Large vessel stroke (e.g. MCA stroke)
- MI + Stroke

4.3 Prophylactic anticoagulants

- Unfractionated Heparin 5000 IU SC TID
- Alternative: Enoxaparin (LMWH) 40 mg SC daily

4.4 BP management

- Lower levels of BP from pre-stroke level is associated with reduction of stroke risk in the future if the stroke is due to atherosclerosis.
- BP treatment should be started after the acute stroke is stabilized (4-5 days after stroke)
- In general, do not give antihypertensive agents in the first 24 hours unless one of the following three conditions is present:
  - The patient’s BP is very high (systolic >220, diastolic >120, or mean arterial pressure >130 mm Hg).
  - The patient has a significant medical indication for antihypertensive therapy. Examples include: Acute MI, Aortic dissection, Severe heart failure, Hypertensive encephalopathy.
- Better anti-hypertensives after stroke are **diuretics; ACE-I** or **CCB.**
- Advice on how to reduce salt intake, limit alcohol intake, avoid licorice and decongestants.
- **Smoking:** Counseling, liberal nicotine replacement therapy, varenicline or bupropion
- **Obesity:** Counseling on caloric restriction, referral to dietitian, bariatric surgery in refractory patients with severe obesity and diabetes mellitus or insulin resistance:
- **Exercise counseling** and high adherence Mediterranean diet

Supportive management for Ischemic stroke

- Administer O_2
- GI prophylaxis for Cushing ulcer
- DVT prophylaxis after 24hrs → early physiotherapy
- Bladder care
- NG tube
- Prevent bedsore
  - ✓ Positioning every 1hr for critical pt and every 2hr for non-critical pt
- Treat comorbidities → MI, UTI, Pneumonia…. which increase metabolic demand of brain and increase 2ry brain injury
- Treat electrolyte disturbance
- Anti-hypertensive
  - ✓ If s/he was on antihypertensive mgt, resume previous dose after 24hr
  - ✓ For new case treat after 7day

  - ✓ For hypertensive urgency use hydralazine, labetalol (beta blocker)
  - ✓ For chronic HTN → ACE-I/ARB or ACE-I/diuretics
- ❖ Physiotherapy
  - ✓ Speech therapy
  - ✓ Physical therapy
  - ✓ Neuro rehabilitation
- ❖ Treat the underlying cause
  - ✓ Cardioembolic stroke → anticoagulant based on CHA_2DVASC_2 score
  - ✓ AF
  - ✓ IE → emergency antibiotic then definitive surgery based on indication

B. Management of hemorrhagic stroke

- Basic and supportive cares are the same as ischemic stroke
- Issues related to treatment of ICH have been dominated by two main considerations:
  1. The type and intensity of medical interventions required to improve the functional and vital prognosis and
  2. The choice between medical and surgical therapy.

- Treatment can be **broadly categorized into**:
  1. Acute medical interventions designed to **decrease hematoma expansion**
  2. Methods to **decrease secondary injury**

Basic medical care

- Patients with a GCS < 8 should be intubated to decrease the risk of aspiration.
- Mechanical ventilation should ensure adequate oxygenation and normal levels of carbon dioxide:
- Airway care and prevention of aspiration if GCS is > 8
- Hyperventilation for acute management of increased ICP. Osmotic therapy should be initiated with mannitol or hypertonic saline.
- Isotonic IV fluids are started and adjusted to correct for any electrolyte abnormalities with the goal of obtaining and maintaining euvolemia.
- Feeding should be initiated as soon as swallow test is performed
- EVD (external ventricular drainage) should be considered in hydrocephalus; IVH; and if CBF (cerebral blood flow) is < 60
- Cardiopulmonary complications are common after ICH and can worsen outcome.
- ECG changes and troponin leaks may be found during ICH but do not appear to affect short-term prognosis: needs to be followed repeatedly.

- Pneumonia and pulmonary edema are the most common pulmonary complications that should be looked for and treated promptly: Fever should be treated
- Pneumatic compression devices and elastic stockings have been shown to be effective preventive treatment for DVT and PTE: Prophylactic Heparin is an alternative
- Continuous EEG should be considered in patients after an intra-cranial hemorrhage that has a disproportionate effect on their level of consciousness: AEDs

1. Attempts to reduce hematoma expansion

- ✓ Most cerebral hemorrhages stopped bleeding within 6 hours.
- ✓ Rapidly reducing the **BP** to < 140/80 mmHg has been associated with reduced hematoma size. Particularly in the 1st 6hrs
- ✓ BP reduction
  - Elevated BP increases ICP and can cause further bleeding. However, hypotension can lower cerebral blood flow, worsening the neurologic deficits. Therefore, **BP reduction must be gradual.**
  - Treatment is indicated if systolic BP is >180 or the MAP is >130.
    - **Labetalol:** Intravenous boluses
      - ❖ Initial dose: 10 to 20 mg IV push over 2 minutes
      - ❖ Until target is achieved give double the initial dose in 15 minutes (maximum dose: 80 mg/dose)
      - ❖ A total maximum dose: 300 mg.

      OR
    - Labetalol Continuous IV infusion: Initial: 0.5 to 2 mg/minute. Titrate the dose to a maximum of 10 mg/minute. A total maximum dose: 300mg
    - **Hydralazine;** 5mg, IV every 20-30 minutes until target BP achieved
- ✓ If there is hemorrhagic transformation give cryoprecipitate
- ✓ **Serum glucose level** should be kept between 100 and 180 mg/dl: Correction doses with insulin

2. Methods to Decrease Secondary Injury

- ✓ A significant amount of the neurologic damage that occurs after ICH can be attributed to secondary processes.
- ✓ A rationale for surgical removal of ICH is to remove the offending substances before secondary damage can develop: Unfortunately, **only a few ICHs are candidates for surgical removal.**
  - Cerebellar hemorrhages > 3 cm in diameter should have surgical evacuation.
- The Minimally Invasive Surgery Plus T-PA for ICH Evacuation
- The Intra-operative CT-Guided Endoscopic Surgery for ICH

- *Look other methods of decreasing 2ry brain injury in ischemic stroke* mgt

Chapter 7; Paraplegia (ከወገብ በታች ሽባነት)

Dr. Mulualem. G

Clinical features and how to write hx of paraplegia

History

- Pt's may present with
    - Failure to use both (R&L) lower extremity (i.e. bilateral lower extremity weakness)
    - Back pain
- Weakness
    - 1st let us remember the terminologies
        - ✓ Monoplegia → weakness of one extremity
        - ✓ Paraplegia → weakness of two extremities (commonly bilateral lower extremities)
        - ✓ Triplegia → weakness of three extremities
        - ✓ Quadriplegia → weakness of four extremities
    - Ask the symmetry → i.e. bilateral in paraplegia
    - From where to where is the progression of weakness
        - ✓ Proximal to distal → weakness starts with
            - Difficulty of raising hand/combing hair
            - Difficulty of standing from sitting position/walking up hails
        - ✓ Distal to proximal → weakness starts with
            - Difficulty of unbuttoning, scissoring
    - Onset → from start of weakness to complete loss of function but not upto hospital arrival
        - ✓ Abrupt (maximal at onset)
        - ✓ Progressive → worsen gradually then complete immobilization
    - Associated with
        - ✓ Numbness → starts in the feet and progress upwards
        - ✓ Burning sensation
        - ✓ Paraesthesia
        - ✓ Cold sensation
        - ✓ Anhidrosis → below the lesion

        - ✓ heaviness
- ➢ Back pain
    - 1st smx mostly
    - Onset → rapid/slow
    - **Localized** over the spine (in non-compressive lesions) or radiate to root distribution like to buttock or LL i.e. **radicular pain** (in compressive lesions)
    - Characterize the pain
        - ✓ Sharp, lancinating, radicular pain, aggravated by coughing, sneezing, or straining → compressive lesions
        - ✓ Dull aching or burning, bund like, localized pain → non compressive
    - Persistent or intermittent
    - Associated with low grade intermittent fever, chills and rigor (e.g. in post viral TM/transverse myelitis/)
        - o N.B if fever is associated with chills and rigor mostly it is high grade fever
- ➢ Preceding infection smx → URTI, GI infections, UTI
- ➢ Incontinence
    - Faces/flatus, urinary incontinence
    - Urgency, hesitancy
    - Constipation, urinary retention
- ➢ Fever
- ➢ Ulceration → with foul smelling discharge
- ➢ Neck stiffness

Risk factors

- ➢ Infection
    - Syphilis → Tabes dorsalis
    - TB → TM (transverse myelitis), TB spondylitis
    - Viral → TM
    - Schistosomiasis
        - ▪ TM, granulomatous disease
        - ▪ S.mansoni and S.hematobium typically infect the spinal cord causing rapidelly progressive TM, affect lower thoracic spinal cord followed by lumbosacral spinal cord
    - Brucellosis
- ➢ Vaccination → GBS from acute rabies vaccine
- ➢ Diet → guaya → neuro-laterization
- ➢ Malnutrition
    - Vitamin B12 deficiency which result in SCDC (severe combined degeneration of the cord), common in vegetarians
    - Vitamin B12 deficiency also occurs in post illeal resection
    - Copper deficiency → Myeloneuropathy

- Trauma → Disc prolapse (common in heavy weight lifters), SDH over the spinal cord
- Occlusion of anterior spinal artery → anterior cord sxx
    - Caused by atherosclerosis, embolism, vasculitis…
    - Other cause of anterior cord sxx is abdominal surgery (rupture of the aorta) → spinal cord infarction
- Malignancy
    - primary or metastasis to spinal cord
    - hematologic malignancy involving vertebral bones
    - other malignancies which metastasize to the back bone like prostate,breast, bronchogenic ca,RCC, GI malignancy
- Family history → ALS (amyotropic lateral sclerosis), hereditary spastic paraplegia
- AF, IE, DCMP, CHF → result in cardiac emboli to anterior spinal artery
- DM → Posterior cord sxx, DSPN (Distal symmetric pyelonephropathy)
- RVI → vascular myelopathy, SCDC

Complication of paraplegia

- DVT
- Aspiration pneumonia
- Bed sore

Sample history

Sample history of a patient from Metema with the DX of paraplegia 2^{ry} to non-compressive myelopathy 2^{ry} to acute transverse myelitis.

Chief compliant

Bilateral lower extremity weakness of 10 hrs duration

HPI

This patient was last relatively healthy 10 hours back, at which time he started to experience sudden onset of bilateral lower extremity weakness while he was sitting with families in a holiday gathering. The weakness was maximal at onset to the extent he failed to stand from sitting position and he was unable to raise, flex or extend the legs by himself. Associated with this he also feels numbness which starts in the feet and progress upwards, burning sensation, Paresthesia, Cold sensation heaviness of the legs, Fecal and urinary incontinence.

Three days prior to the onset of weakness, he experienced persistent, dull aching, bund like type of back pain which is localized over the spine area without any aggravating and relieving factors associated with low grade intermittent fever without chills or rigor. For this he visited a local clinic at metema where he was given unspecified antipain, and red oval tablets to be taken 3 times per day. He got improvement for the pain and he visited metema primary hospital when he sustained weakness and after catheterization he was referred immediately to our hospital for better investigation and management.

- He is unmarried daily laboror and has hx of unsafe sexual practice with multiple sexual partners but no genital ulcer or penile discharge *(tabes dorsalis/tertiary syphilis/ i.e. posterior cord sxx, post viral TM, RF for herepes zoster)*
- NO hx of chronic cough, contact with chronic cougher or a known TB patient *(TM /transverse myelitis/, TB spondylitis]*
- No hx of vaccination *(GBS from acute rabies vaccine)*
- He/she usually eats injera made of "teff" and "machilla" and "wott" made of "atter" and "dagusa" 3-4 times per day. Occasionally he/she eats meat during holidays *(guaya → neurolateralization, vitamin B12 deficiency → SCDC, copper deficiency → myeloneuropathy)*
- No hx of smoking or chronic alcohol intake
- No hx of river water contact (RWC) or post RWC itching *(schistosomiasis)*
- No hx of abdominal surgery *(rupture of the aorta → spinal cord infarction)*
- No hx of pesticide or herbicide exposure, radiotherapy to the back *(Lymphoma is the commonest cause of compressive myelopathy, radiation myelopathy)*
- No hx of Bone pain, epistaxis, swelling over the neck, axilla or groin *(hematologic malignancy involving vertebral bones, also r/o other malignancies which metastasize to the back bone like prostate, breast, bronchogenic ca, RCC, GI malignancy)*
- No hx of trauma to the back *(SDH over the spinal cord)*
- No family hx of similar illness *(ALS, hereditary spastic paraplegia)*
- No hx of dspnea, orthopnea, PND or palpitation *(cardiac emboli resulting in anterior spinal cord sxx)*
- No hx of tinnitus, blurring of vision or light headedness *(Vitamin B12 deficiency → SCDC)*
- NO hx of DM, HTN or asthma *(DM cause posterior cord sxx without weakness)*
- Screened for RVI and found to be NR *(GBS, TM, Vascular myelopathy, SCDC)*

Finally, S/he was admitted to our hospital supported physically by his families

Physical examination (pertinent findings)

1 GA

2 Vital signs

- OHT
- Tachycardia

> - GBS or other causes of autonomic dysfunction
> - In compressive myelopathy autonomic dysfunction happens late in the disease progression since autonomic pathway is in the center of spinal cord which will be affected later when the mass is huge enough

- Tachypnea

  - Pulmonary embolism from DVT which intern result from prolonged immobilization due to paraplegia
  - Diaphragmatic paralysis (characterized by paradoxical respiratory movement)
- Arrythmia → AF is RF for embolism which results in anterior cord sxx

3 HEENT → anaemia 2ry to vitamin B12 deficiency

4 LGS

- Breast ca features
- Cervical LAP from lymphoma which result in compressive myelopathy
- Anhidrosis and sweat level

5 RS

- TB features → check TB findings in all systems
- Consolidation from aspiration pneumonia

6 CVS

- CHF features, IE, DCMP → cardiac emboli → anterior cord sxx

7 Abdominal examination

- Abdominal distension from fecal or urinary retension
- Constipation
- DRE → features of prostatic ca which metastasize to back bone

8 GUS

- Urinary retention
- Sexual dysfunction

9 MSS

- Spinal tenderness especially point tenderness in disc prolapse
- Gibbus with deformity in TB
- Bed sore, DVT → CXN

11 **IS** → pallor from vitamin B12 deficiency

12 **NS**

- Atrophy (wasting)
- Hypo/hypertonic
- Hypo/hyperreflexia, areflexia
- Power
  - 0/5 & 1/5 → plegia
  - 2/5 - 4/5 → paresis
  - 5/5 → normal
- Sensory and sweat level
- Position and vibration sensation loss in posterior cord disorders
- Pain and temperature sensation loss in anterior cord disorders
- Autonomic dysfunction (like incontinence) in central cord involvement
- Absent superficial reflexes especially abdominal and cremasteric reflex

- Stiff neck → cervical spondylosis

DDX

DDX of Paraplegia

UMNL			LMNL
Brain	Spinal cord		
	Compressive	non-compressive	

- **Parasagittal sinus thrombosis**
- **Mass over the parasagittal area**
- ACA stroke
- Hydrocephalus
	- **Primary spinal cord tumours**
	  ○ Intramedullary
	    ▪ Ependymoma
	    ▪ Astrocytoma
	  ○ Extramedullary
	    ▪ Neurofibroma
	    ▪ Meningioma
	    ▪ schwannoma
	- 2ry spinal cord tumours (metastasis to spinal cord)
	  ○ Bronchogenic ca
	  ○ Breast ca
	  ○ Prostatic ca
	  ○ Lymphoma
	  ○ Multiple myeloma
	  ○ GI cancers
	  ○ RCC
	- Granulomatous infections
	  ○ **TB**
	  ○ **Schistosomiasis**
	  ○ CTD (connective tissue disease)
	  ○ Brucellosis
	- **Disc prolapse (herniation)**
	- **Syringomyelia**
	- **Epidural abscess in spinal cord**
	- Sarcoidosis
	- Early stage of foramen magnum sxx
	- Spinal stenosis
		- Infectious
		  ○ **TM (transverse myelitis)**
		  ○ **Neurosyphilis (tabes dorsalis)**
		  ○ Rabies vaccine
		  ○ HSV2, CMV, EBV, HIV, HTLV
		  ○ Lyme disease
		- Metabolic
		  ○ Vitamin B12 deficiency → SCDC
		- Vascular (Spinal cord syndromes)
		  ○ Anterior spinal cord sxx (Spinal cord infarction)
		  ○ Posterior cord SXX
		  ○ Central cord sxx
		  ○ **BSS**
		  ○ Complete cord transaction
		  ○ Cauda equina sxx and conus medullaris → LMNL
			- Plexopathy
			- Radiculopathy
			  ○ Bilateral poliomyelitis
			- Neuropathy
			- NMJ disorders
			  ○ Myasthenia gravis
			- Myopathy
			- **GBS**
			- Cauda equina sxx
			- Conus medullaris
			- MND (motor neuron disease)

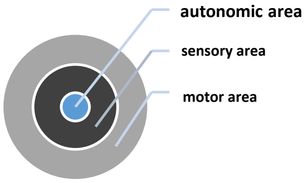
Mixed			
Have mixed features of UMNL and LMNL - ALS - MS - Spinal shock - SCDC			

DDX of paraplegia based on onset of illness	
Acute causes	**Chronic causes**
TM GBS Disc prolapse Spinal cord infarction Epidural abscess	ALS Peripheral neuropathy Granulomatous infections Metastatic tumours Primary spinal cord tumours Cervical spondylosis

- UMNL (upper motor neuron lesion)
  - ✓ Brain
    - **Parasagittal sinus thrombosis**
    - **Mas over the parasagittal area**
    - Hydrocephalus
    - ACA stroke
  - ✓ Spinal cord

N.B

Spinal cord lesions can be compressive or non-compressive. Let us see their difference with the characteristic presentation.

Compressive	non-compressive
➢ Back pain - **radicular pain** radiates to root distribution. For example, to buttock or LL - Sharp, lancinating, radicular pain, aggravated by coughing, sneezing, or straining ➢ 1st pt present with back pain then progress sequentially to weakness → sensory loss → autonomic dysfunction (like urinary incontinence and sexual dysfunction). This is due to horizontal localization in spinal cord.  Image. Spinal cord horizontal localization	➢ **Back pain** - **Localized** over the spine - Dull aching or burning, bund like, localized pain ➢ After back pain all other manifestations like weakness, sensory loss and autonomic dysfunction may happen at the same time especially in complete cord involvement. Typical example is TM. ➢ Separate sensory loss is cmn in non-compressive lesions. For example - Pain and temperature loss → anterior cord sxx - Position and vibration loss → posterior cord sxx

Compressive

- Primary **spinal cord tumours**
  - ➢ Intramedullary → sphincter abnormality is the earliest manifestation
    - Ependymoma
    - Astrocytoma

  - extramedullary
    - neurofibroma
    - meningioma
    - schwannoma
- secondary spinal cord tumours (metastasis to spinal cord)
  - Bronchogenic ca
  - Breast ca
  - Prostatic ca
    - Commonly involve lumbosacral area
    - **Osteoblastic** tumour unlike all other malignancies (osteolytic)
  - Lymphoma
  - Multiple myeloma
  - GI cancers
  - RCC
- Granulomatous infections
  - **TB** → can cause of TM
    - TB spondylitis a.k.a pott's disease
    - **Gibbus** (wedge shaped fusion of two vertebrae) deformity is typical feature
    - Usually occur in the absence of extra spinal TB
    - Cmn in lower thoracic and upper lumbar area
  - **Schistosomiasis**
  - CTD (connective tissue disease)
  - brucellosis
- **Disc prolapse (herniation)**
  - Heavy weight lifters and overweight are at risk
  - C/F → chronic low back pain and prolonged weakness
- **Syringomyelia**
  - Cavity formation within the cord
  - Chronic and progressive
  - Caused by Acquired or congenital factors (acquired causes can be from post infectious, trauma/from hyperextended neck during caring objects by head/)
  - Spare the posterior column
  - Sensory loss (pain and temperature loss) involved
  - There is wasting of small hand muscles
- Sarcoidosis
- **Epidural abscess in spinal cord**
  - Triads include fever, back pain and FND (Paraplegia)
  - Tender over the involved area
  - There may be Sensory level
  - Cmn in immunocompromised pt's
  - Staphylococcus is the cmn etiologic agent
- Early stage of foramen magnum sxx → Clock wise rotation of weakness
- Spinal stenosis

Non compressive

- infectious
  - **TM (transverse myelitis)**
    - Sudden, rapid weakness which manifest with in hrs to days
    - Present with fever, back/limb pain followed by sensory level, bladder disturbance within hrs
    - Usually happens following infection with MMRV (measles, mumps, rubella, varicella), EBV, CMV, influenza virus
    - Having sharp sensory level differentiate it from GBS
    - DX criteria
      - Bilateral motor, sensory and autonomic dysfunction occurring simultaneously
      - Sensory level
      - Progression to nadir of clinical deficit between 4hrs and 21 days of onset
      - Exclusion of compressive, post radiation, neoplastic and vascular causes
  - **Neurosyphilis → tabes dorsalis**
    - Cause posterior cord sxx
      - No weakness
      - Pain and temperature preserved
      - Only position and vibration sensation lost
    - Happen after 2-3 decades of syphilis infection unless congenital syphilis
  - Rabies vaccine
  - HSV2, CMV, EBV, HIV, HTLV
  - Lyme disease
- Metabolic
- Vitamin B12 deficiency → SCDC
- Vascular (Spinal cord syndromes)
- Anterior spinal cord sxx (Spinal cord infarction)
    - Rare, if it occurs commonly occur in mid thoracic spinal cord (water shed area)
    - Common in anterior spinal cord because anterior spinal artery is single artery unlike posterior spinal cord arteries
    - Spare position and vibration sensation
    - More sudden in onset than TM
    - RF include cardiogenic emboli, thrombus, vasculitis, hypotension, atherosclerosis, aortic dissection
- Posterior cord SXX
- Central cord sxx
- **BSS**
- Complete cord transaction
- Cauda equina sxx and conus medullaris → LMNL
- LMNL (lower motor neuron lesion)
  - ✓ Plexopathy
  - ✓ Radiculopathy

    - Bilateral poliomyelitis
        - Typically affect anterior horn
        - Acute in onset
  - ✓ Neuropathy
  - ✓ NMJ disorders
    - Myasthenia gravis
  - ✓ Myopathy
  - ✓ **GBS**
    - Variants of GBS include
        - AMAN (acute motor axonal neuropathy)
        - ASMAN (acute sensorimotor axonal neuropathy)
        - AIDP (acute inflammatory demyelinating polyradiculoneuropathy)
        - MFS (Miller Fisher syndrome)

        Nowadays CIDP (chronic inflammatory demyelinating polyradiculoneuropathy) **is out of GBS variant**
    - 8 A's of GBS
        - ○ **Autoimmune**
        - ○ **Areflexia**
        - ○ **Ascending paralysis**
        - ○ **Acute**
        - ○ **Afebrile**
        - ○ **Absence of sensory level**
        - ○ **Autonomic involvement** → OHT, **arrythmia**
        - ○ **Acellular CSF** (albumin cytogenic dissociation → decreased number of cells but, increased protein/albumin of CSF)
  - ✓ Cauda equina sxx
  - ✓ Conus medullaris
  - ✓ MND (motor neuron disease)
    - Spare sensory system
    - Idiopathic
    - Cmn in old age pt's (>55)
    - Chronic in onset
    - Initially Unilateral which progress to the other side
    - e.g. bulbar palsy, ALS (corticospinal + anterior horn cell degeneration), primary lateral sclerosis (only cortico spinal tract degeneration)

- ❖ Mixed
  - ✓ ALS
  - ✓ MS
  - ✓ Spinal shock
  - ✓ SCDC
    - If the lesion is in thoracic area it cause paraplrgia, if it is in cervical area it cause quadriplegia
    - Present with
        - ascending parasthesia (tingling, numbness)
        - glove and stocking pattern

IX

1. Spinal X-ray
    - Request to the target level depending on the site of lesion (for example if lesion is at T8 with sensory level at T10 the request should be *''thoracic veretebral X-ray centered at T8''*)
    - Important for
        - **Gibbus** in TB (TB spondylitis) → wedge shaped fusion of lower part of the upper vertebrae and upper part of the lower vertebrae (*if you suspect TB spondylitis do Spinal x-ray, CBC, ESR, CXR and other TB work up)*
        - Herniated inter vertebral disc
        - 2ry deposit of malignancy
            - Osteblastic in prostatic ca but osteolytic in other malignancies
        - Fracture or dislocation of vertebrae, bone density
        - Cervical spondylosis
2. Spinal MRI
    - Ix of choice which confirm the site of lesion
        - Have excellent anatomic resolution and extent of tumour
    - Distinguish between malignancy and other lesions like epidural abscess, tuberculoma, epidural haemorrhage
    - If MRI is not available do CT myelography
        - Permit CSF analysis
3. ESR and blood culture → for epidural abscess
4. CBC
    - Megaloblastic Anaemia in vitamin B12 deficiency (low hemoglobin with MCV > 100)
    - Leucocytosis in epidural abscess and malignancy
    - Multiple myeloma → plasmacytosis
5. CSF analysis

- Low opening pressure
- Acellular CSF (albumin cytogenic dissociation → No cell/decreased number of cells but, increased protein/albumin of CSF) in GBS
- Xanthochrome
- Important for epidural abscess

6. PICT → SCDC, TM
7. RBS → DSPN (distal symmetric polyneuropathy) characterized by glove and stocking pattern
8. Nerve conduction test (NCT) → neuropathy
9. Muscle biopsy → from largest muscle involved for myopathy dx
10. S/E → TM, GI source of infection like campylobacter in GBS
11. U/A and urine culture → TM

12. BUN & creatinine
13. Tumour markers

Discussion

1.1 Localization of neurologic disorders

- ➢ Neuro-localization is Identification of what site of the nervous system has been affected:
- ➢ Two Pillars for the Diagnosis of neurologic disorders
  1) **Where is the lesion?** → Anatomic diagnosis
     - ✓ CNS
       - ▪ Cortex
       - ▪ Subcortical areas
       - ▪ Brainstem
       - ▪ Spinal cord
     - ✓ PNS
       - ▪ Nerve Root lesion (radiculopathy)
       - ▪ Plexus lesion (plexopathy)
       - ▪ Peripheral nerve lesion
       - ▪ Multifocal or diffuse Peripheral Neuropathy
       - ▪ NMJ and Muscles
  2) **What is the lesion?** → Pathologic diagnosis
     - ✓ Vascular lesions
     - ✓ Infectious lesions
     - ✓ Inflammatory lesions
     - ✓ Neoplastic disorders
     - ✓ Demyelinating lesions
     - ✓ Degenerative disorders
     - ✓ Hereditary abnormalities
     - ✓ Deficiency and Metabolic
     - ✓ Toxin and Drug related

Distinction between CNS and PNS lesions

Signs and symptoms	CNS lesions (UMNL)	PNS lesions (LMNL)
Pain	Headache; Neuropathic pain are not common; Central pain	Neuropathic pain; Distorted sensation like allodynia
Pattern of weakness	CST distribution weakness; Hemi body distribution;	Symmetric weakness; Very focal weakness; Myotomal weakness
Pattern of sensory loss	Hemi distribution sensory loss; Dissociated sensory Sx, Sensory	Stocking-glove; Fiber type Dermatome distribution
Reflexes	Hyperreflexia, pathologic reflex and loss of coetaneous reflex	Areflexia; Hyporeflexia or normal coetaneous reflex are spared
Tone	Spastic, rigidity; paratonia	Normal or flaccid; Myotonia
Cranial nerve	Incomplete lesions	Complete; often bilateral

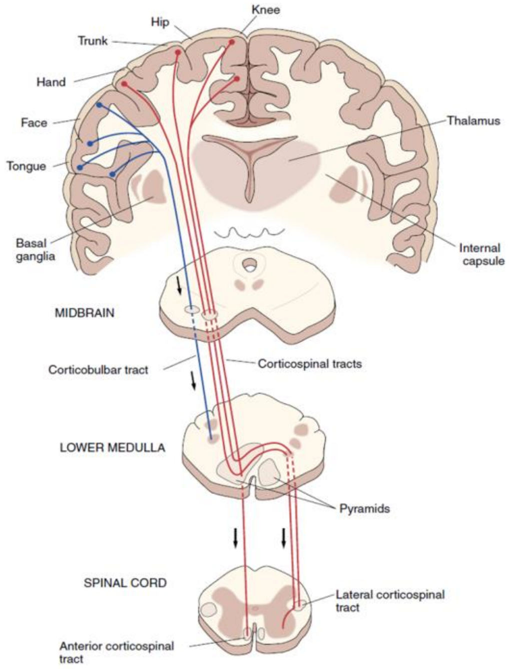
Mental affection	Can occur depending on the area of affection	Very rare
Others	Cortical signs; Cerebellar signs…	Atrophy; Fasciculation; Spasms….

Regional localization

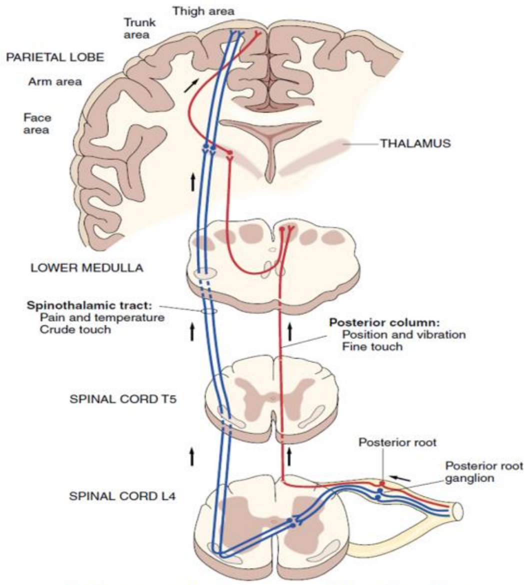
- If UMNL
  - ✓ The cortex; hemispheres
  - ✓ Subcortical white matter
  - ✓ Diencephalon; basal ganglia, thalamus
  - ✓ Brain stem
  - ✓ Spinal cord
- If LMNL
  - ✓ Spinal nerves
  - ✓ Plexus
  - ✓ Peripheral nerve
  - ✓ NMJ
  - ✓ Muscle
- Interpret the characteristic **motor, Gait and sensory abnormality** to locate regional neurologic disease.
- Use the specific function of region for best localization.
- For example: Cortical functions like speech, cortical sensory function**Regional**

Motor localization

- CST (corticospinal tract) and CBT (corticobulbar tract) originates from pre-central frontal gyrus called **motor nucleus**

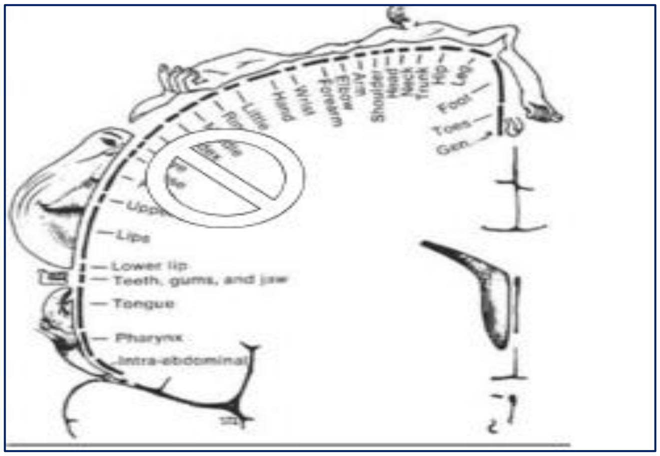

Knee
Hip
Trunk
Hand
Face
Tongue
Thalamus
Basal ganglia
Internal capsule
MIDBRAIN
Corticobulbar tract
Corticospinal tracts
LOWER MEDULLA
Pyramids
SPINAL CORD
Lateral corticospinal tract
Anterior corticospinal tract

MOTOR PATHWAYS: CORTICOSPINAL AND CORTICOBULBAR TRACTS


Thigh area
Trunk area
PARIETAL LOBE
Arm area
Face area
THALAMUS
LOWER MEDULLA
Spinothalamic tract:
Pain and temperature
Crude touch
Posterior column:
Position and vibration
Fine touch
SPINAL CORD T5
Posterior root
Posterior root ganglion
SPINAL CORD L4

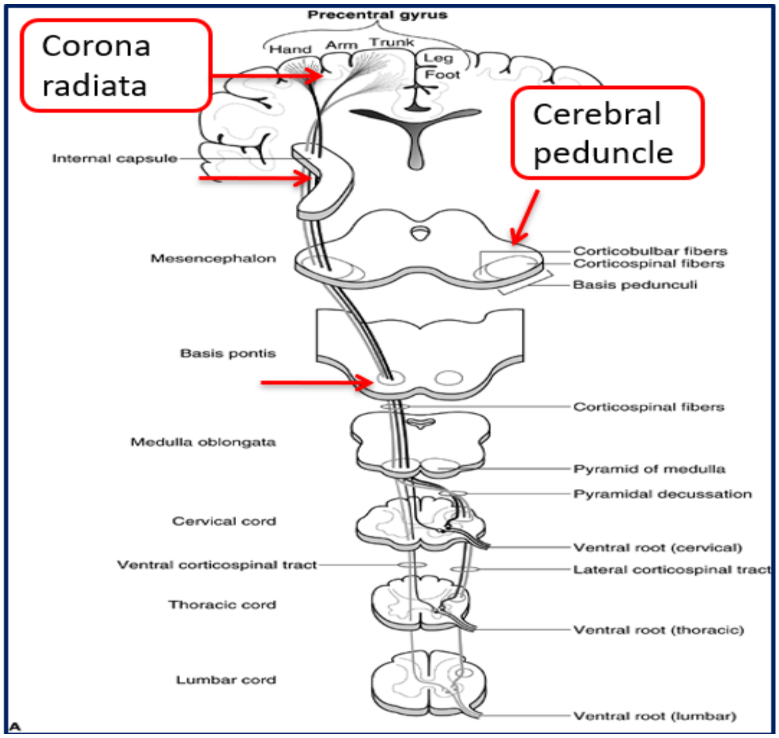
SENSORY PATHWAYS: SPINOTHALAMIC TRACT AND POSTERIOR COLUMNS

- The motor fibers are somatotopically organized in patterns that reflect their functional importance: **Motor homunculus**
  - ✓ Medial to lateral: Bladder function — legs — arms — face — oro-buchal


Little
Ring
Hand
Wrist
Elbow
Forearm
Arm
Shoulder
Head
Neck
Trunk
Hip
Leg
Foot
Toes
Gen.
Upper
Lips
Lower lip
Teeth, gums, and jaw
Tongue
Pharynx
Intra-abdominal

Picture; Motor homunculus

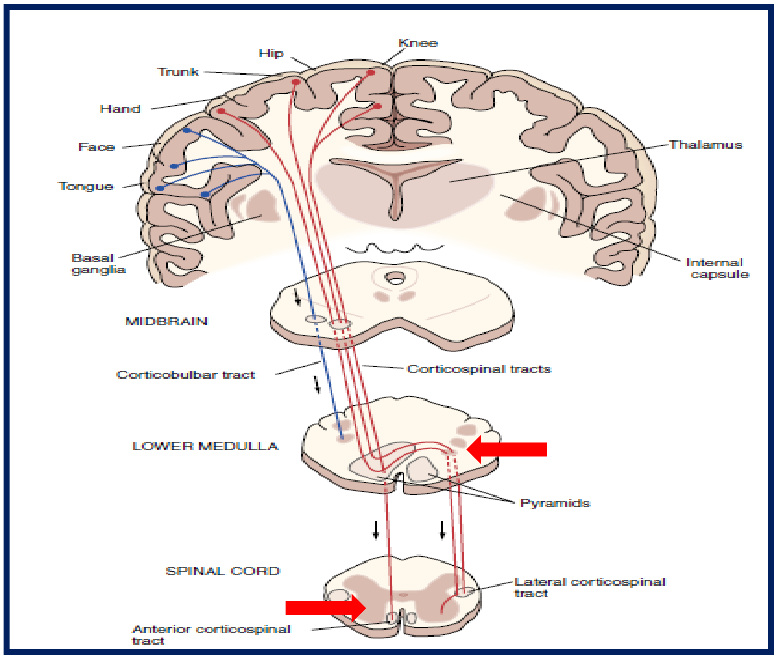
- **Differential weakness** (difference in grade of weakness between UL and LL): CST disorder
- **Transverse Localization:** Signs and symptoms of cortical lesion like aphasia; seizure; cognition


Precentral gyrus
Hand
Arm
Trunk
Leg
Foot
Corona radiata
Cerebral peduncle
Internal capsule
Mesencephalon
Corticobulbar fibers
Corticospinal fibers
Basis pedunculi
Basis pontis
Corticospinal fibers
Medulla oblongata
Pyramid of medulla
Pyramidal decussation
Cervical cord
Ventral root (cervical)
Ventral corticospinal tract
Lateral corticospinal tract
Thoracic cord
Ventral root (thoracic)
Lumbar cord
Ventral root (lumbar)
A

Picture; Motor function localization

- CST and CBT progress down wards via **corona-radiata** as the fibers dispersed widely before reaching the internal capsule: **Differential hemiparesis (arm > face > leg, or vice versa)**
- In the **internal capsule**, the CST and CBT converge independently to rest at the posterior limb and genu of internal Capsule: **Dense hemiparesis**

- In the **brainstem**: CST and CBT join together to pass through cerebral peduncle and basis pontis: **Dense hemiparesis and bulbar palsy**
- **Transverse localization:** CBT are crossed in the brainstem before supplying CN nuclei.


Hip
Knee
Trunk
Hand
Face
Tongue
Basal ganglia
Thalamus
Internal capsule
MIDBRAIN
Corticobulbar tract
Corticospinal tracts
LOWER MEDULLA
Pyramids
SPINAL CORD
Lateral corticospinal tract
Anterior corticospinal tract

Picture; Motor function localization

- **At the medulla:** CST cross the midline to the opposite side to run to the respective level of the spinal cord
- At the point of decussation, crossed and uncrossed fibers are found near each other which can result various types of weaknesses: **Crural paresis, diplegia, hemiplegia, quadriplegia** depending on the specific location.
- **At the spinal cord** CST ends to excite the alpha motor N: **Paraplegia; quadriplegia**
- **Transverse Localization:** The lower four CN lesions cause crossed paralysis with body weakness

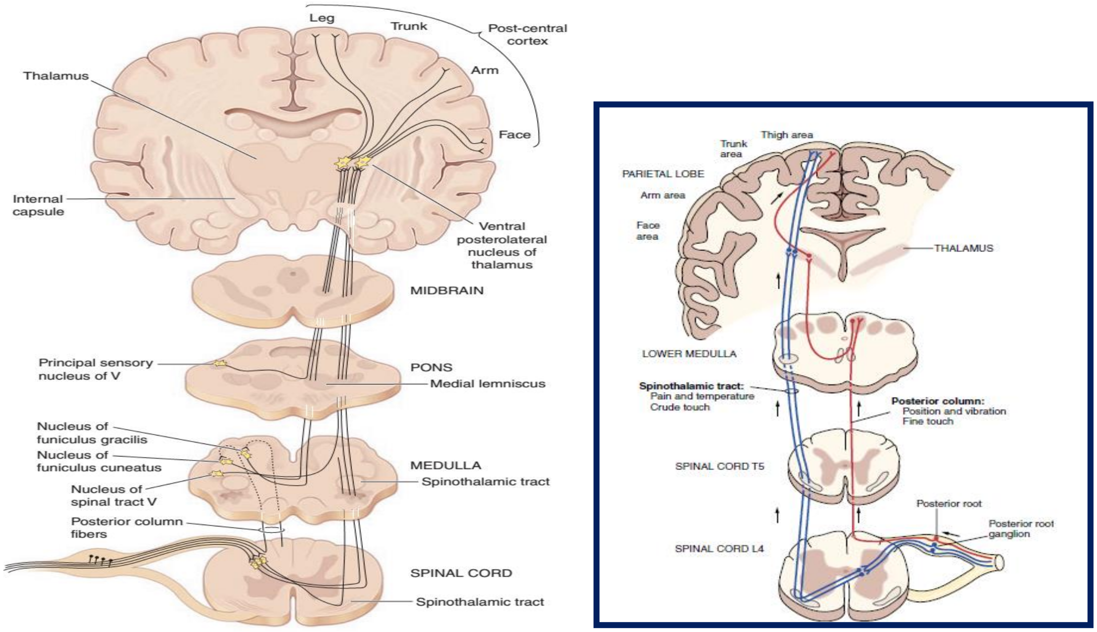
Extra-pyramidal control of motor function

- CST and CBT projections to the basal ganglia and cerebellum have an active role in the planning and execution of movements.
- The cerebellum and basal ganglia are critically important for coordinated and organized finely tuned motor functions
- The **cerebellum** has a major role in the coordination of movements and control of equilibrium and muscle tone. The cerebellum controls the ipsilateral limbs through connections with the SC and BS; but opposite to the cortex → **Ataxia**
- The **basal ganglia** play a major role in the control of posture and movt. Participate in motor planning through reciprocal connections. The cortico-striate pathway includes direct and indirect projections from the cerebral cortex to the striatum → **movement disorders**

Table; Summary Of UMNL	
Location of the injury	**Pattern and distribution of motor weakness**
Cortex	Signs and symptoms of cortical lesion like **aphasia; seizure; cognition**
Corona radiata	Differential hemiparesis
Internal capsule	Dense hemiparesis
Brainstem	Dense hemiparesis and bulbar palsy
Spinal cord	Paraplegia (lower thoracic and lumbosacral cord injury); quadriplegia (mainly cervical and rarely higher thoracic cord injury)

Table; Summary Of LMNL	
Location of the injury	**Pattern and distribution of motor weakness**
Spinal nerves	Myotomal muscle weakness often not recognized
Plexus	Monoparesis affecting only one limb
Single nerve	Weakness of the muscles that are supplied by the affected nerve
Diffuse affection of many nerve fibers	Distal symmetric; Proximal symmetric muscles of the limbs are involved.

Regional localization of the Sensory system


Leg
Trunk
Post-central cortex
Arm
Face
Thalamus
Internal capsule
Ventral posterolateral nucleus of thalamus
MIDBRAIN
Principal sensory nucleus of V
PONS
Medial lemniscus
Nucleus of funiculus gracilis
Nucleus of funiculus cuneatus
Nucleus of spinal tract V
Posterior column fibers
MEDULLA
Spinothalamic tract
SPINAL CORD
Spinothalamic tract
Thigh area
Trunk area
PARIETAL LOBE
Arm area
Face area
THALAMUS
LOWER MEDULLA
Spinothalamic tract:
Pain and temperature
Crude touch
Posterior column:
Position and vibration
Fine touch
SPINAL CORD T5
Posterior root
Posterior root ganglion
SPINAL CORD L4

Figure; **left) The main somatosensory pathways.** The spinothalamic tract (pain, thermal sense) and the posterior column—lemniscal system (touch, pressure, joint position) are shown. Offshoots from the ascending anterolateral fasciculus (spinothalamic tract) to nuclei in themedulla, pons, and mesencephalon and nuclear terminations of the tract are indicated.

Table; Regional localization of the Sensory system

Location in the NS	Characteristics sensory loss distribution
Peripheral nerve lesions	Sensory loss generally **confined to the area supplied by the nerve**; sensory loss of the whole limb; dermatomal pattern or symmetric distal sensory distribution
Spinal cord lesions	Distinct **sensory level** with all modalities; isloated loss of pain and temperature; isolated vibration and position loss; cape in shoulder distribution; hemicord pattern
Brainstem lesions	**Contralateral pain and temperature loss to the CN palsy and sensation of the face**; **Contralateral vibration and position loss** to the CN palsy
Thalamus	**Contral-lateral hemi sensory loss of all modalities** which includes the face; complex hemi-sensation loss; Central pain
Cortex	**Hemisensory loss with differential sensory loss**; cortical sensory loss; complex sensory loss…

Table; Transverse localization

Location in the NS	Motor	Sensory	Specific
Spinal cord	✚ Distal weakness predominates ✚ Paraparesis, quadriparesis, syringomyelic pattern, hemiparesis or monoparesis. ✚ Weakness is spastic with pathologic reflexes and loss of cutaneous reflexes ✚ Segmental LMNL pattern at the site of the lesion	➢ Sensory level with all modalities; tingling; numbness; parasthesisa; back pain ➢ Pattern specific: Brown-sequard, posterior cord…	✚ Bladder and bowel involved ✚ Lhermitt's sign ✚ sweat level ✚ sensory level ✚ vertebral tenderness
Brainstem	✚ Contra-lateral hemi-weakness; may or may not involve the face ✚ Medullary and bilateral brainstem lesions could have various forms of weakness. ✚ Spastic type of weakness; weakness often dense ✚ Depending on the location of the lesion crossed cranial nerve palsy. M2; P4; MD;4	➢ Lateral: Contra-lateral pain and temp. sense loss with crossed pain and temp loss on the face ➢ Medial: Contra-lateral vibration and position loss	✚ Crossed deficit ✚ Gaze palsy ✚ Loss of consciousness if RF affected ✚ Vertigo ✚ Bulbar affection ✚ Nausea Vomiting…
Thalamus and internal capsule	✚ Weakness is solely because of **Internal Capsule** affection ✚ Weakness is often dense with affection of CN and the face on the same side of the body weakness; spastic type of weakness	➢ Sensory dysfunction is solely a result of thalamic lesion ➢ Contra-lateral sensation loss in all modalities and involve the face; sensory hemiataxia ➢ Complex sensory affection; hemi-inattention	✚ Gaze palsy ✚ sub-cortical aphasia ✚ emotional facial palsy ✚ cognitive decline ✚ sleep disturbance ✚ coma ✚ Thalamic pain syndrome

			movement disorders
Cortex	Weakness is hemi distribution; differential weakness: arm > face > leg, or vice versa Spastic weakness Complex motor function are affected; planned motor activity; motor memory…	➢ Hemisensory loss; differential sensory loss ➢ Complex sensory function are affected: extinction; stereognosis; neglect;	Higher cortical function Apraxia Aphasia visual field defects anosmia seizure…. CN I&II

1.2 Diseases of the Spinal Cord

- Diseases of the spinal cord produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system. Because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and limbs.
- Many spinal cord diseases are reversible if recognized and treated at an early stage; thus, they are among the most critical of neurologic emergencies.
- The efficient use of diagnostic procedures, guided by knowledge of the anatomy and the clinical features of spinal cord diseases, is required to maximize the likelihood of a successful outcome.

Treatable Spinal Cord Disorders

- Compressive
  - ✓ Epidural, intradural, or intramedullary neoplasm
  - ✓ Epidural abscess
  - ✓ Epidural hemorrhage
  - ✓ Cervical spondylosis
  - ✓ Herniated disk
  - ✓ Posttraumatic compression by fractured or displaced vertebra or hemorrhage
- Vascular
  - ✓ Arteriovenous malformation and dural fistula
  - ✓ Antiphospholipid syndrome and other hypercoagulable states
- Inflammatory
  - ✓ Multiple sclerosis
  - ✓ Neuromyelitis optica
  - ✓ Transverse myelitis
  - ✓ Sarcoidosis
  - ✓ Sjögren-related myelopathy
  - ✓ SLE-related myelopathy
  - ✓ Vasculitis
- Infectious
  - ✓ Viral: VZV, HSV-1 and 2, CMV, HIV, HTLV-1, others
  - ✓ Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others

- ✓ *Mycoplasma pneumoniae*
- ✓ Parasitic: schistosomiasis, toxoplasmosis, cystercercosis

- Developmental
  - ✓ Syringomyelia
  - ✓ Meningomyelocele
  - ✓ Tethered cord syndrome
- Metabolic
  - ✓ Vitamin B_{12} deficiency (subacute combined degeneration)
  - ✓ Copper deficiency

Spinal cord Anatomy relevant to clinical signs

- The spinal cord has 31 segments, each defined by an exciting ventral motor root and entering dorsal sensory root.
- The mature spinal cord ends at approximately the first lumbar vertebral body.
- The lower spinal nerves take an increasingly downward course to exit via intervertebral foramina.
- The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies because of the presence of eight cervical spinal cord segments but only seven cervical vertebrae (see table below).
- These relationships assume particular importance for localization of lesions that cause spinal cord compression.
- **Sensory loss below the circumferential level of the umbilicus, for example, corresponds to the T10 cord segment but indicates involvement of the cord adjacent to the 7th or 8th thoracic vertebral body.**
- In addition, at every level, the main ascending and descending tracts are somatotopically organized with a laminated distribution that reflects the origin or destination of nerve fibers.

Spinal Cord Levels Relative to the Vertebral Bodies

Spinal Cord Level	Corresponding vertebral body
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2 - 3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

Determining the Level of the Lesion

- The presence of a horizontally defined level (***sensory level)*** below which sensory, motor, and autonomic function is impaired is a hallmark of a lesion of the spinal cord.
- Sensory loss below this level is the result of **damage to the spinothalamic tract on the opposite side**, **1 to 2 segments higher** in the case of a **unilateral spinal cord lesion**, and **at the level of a bilateral lesion.**

  - ✓ The discrepancy in the level of a unilateral lesion is the result of the course of the second-order sensory fibers, which originate in the dorsal horn, and ascend for one or two levels as they cross anterior to the central canal to join the opposite spinothalamic tract.
- Lesions that transect the descending corticospinal and other motor tracts cause paraplegia or quadriplegia with heightened deep tendon reflexes, Babinski signs, and eventual spasticity (the upper motor neuron syndrome).
- Transverse damage to the cord also produces autonomic disturbances consisting of absent sweating below the implicated cord level and bladder, bowel, and sexual dysfunction.
- The uppermost level of a spinal cord lesion can also be localized by attention to the *segmental signs* corresponding to disturbed motor or sensory innervation by an individual cord segment.
  - ✓ A band of altered sensation (hyperalgesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a muted or absent deep tendon reflex may be noted at this level.
  - ✓ These signs also can occur with focal root or peripheral nerve disorders; thus, they are most useful when they occur together with signs of long tract damage.
- With severe and acute transverse lesions, the limbs initially may be flaccid rather than spastic.
  - ✓ This state of “**spinal shock**” lasts for several days, rarely for weeks, and may be mistaken for extensive damage to the anterior horn cells over many segments of the cord or for an acute polyneuropathy.
- The main features of transverse damage at each level of the spinal cord are summarized below.

Cervical Cord

- ➢ Upper cervical cord lesions produce quadriplegia and weakness of the diaphragm.
- ➢ The uppermost level of weakness and reflex loss with lesions at C5-C6 is in the biceps; at C7, in finger and wrist extensors and triceps; and at C8, finger, and wrist flexion.
- ➢ Horner’s syndrome (miosis, ptosis, and facial hypohidrosis) may accompany a cervical cord lesion at any level.

Thoracic Cord

- Lesions here are localized by the sensory level on the trunk and, if present, by the site of midline back pain.
- **Useful markers of the sensory level on the trunk are the nipples (T4) and umbilicus (T10).**
- Leg weakness and disturbances of bladder and bowel function accompany the paralysis.
- Lesions at T9-T10 paralyze the lower–but not the upper–abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (*Beevor’s sign*).

Lumbar Cord

- Lesions at the L2-L4 spinal cord levels paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex.
- Lesions at L5-S1 paralyze only movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerks (S1).

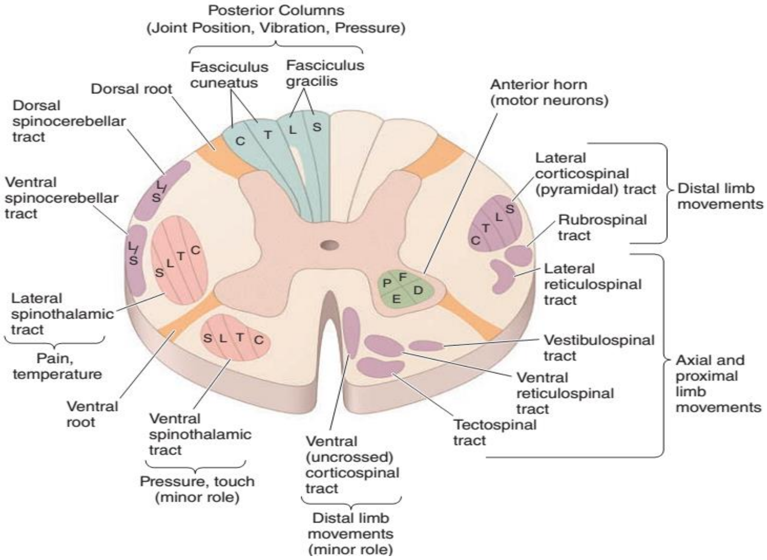
Sacral Cord/Conus Medullaris syndrome

- The conus medullaris is the tapered caudal termination of the spinal cord, comprising the sacral and single coccygeal segments.
- The distinctive conus syndrome consists of;
  - ✓ Bilateral saddle anesthesia (S3-S5)
  - ✓ Prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and
  - ✓ Impotence.
- The bulbocavernosus (S2-S4) and anal (S4-S5) reflexes are absent.
- Muscle strength is largely preserved. By contrast, lesions of the cauda equina, the nerve roots derived from the lower cord, are characterized by low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function.
- Mass lesions in the lower spinal canal often produce a mixed clinical picture with elements of both cauda equina and conus medullaris syndromes.

Cauda equina syndrome (CES)

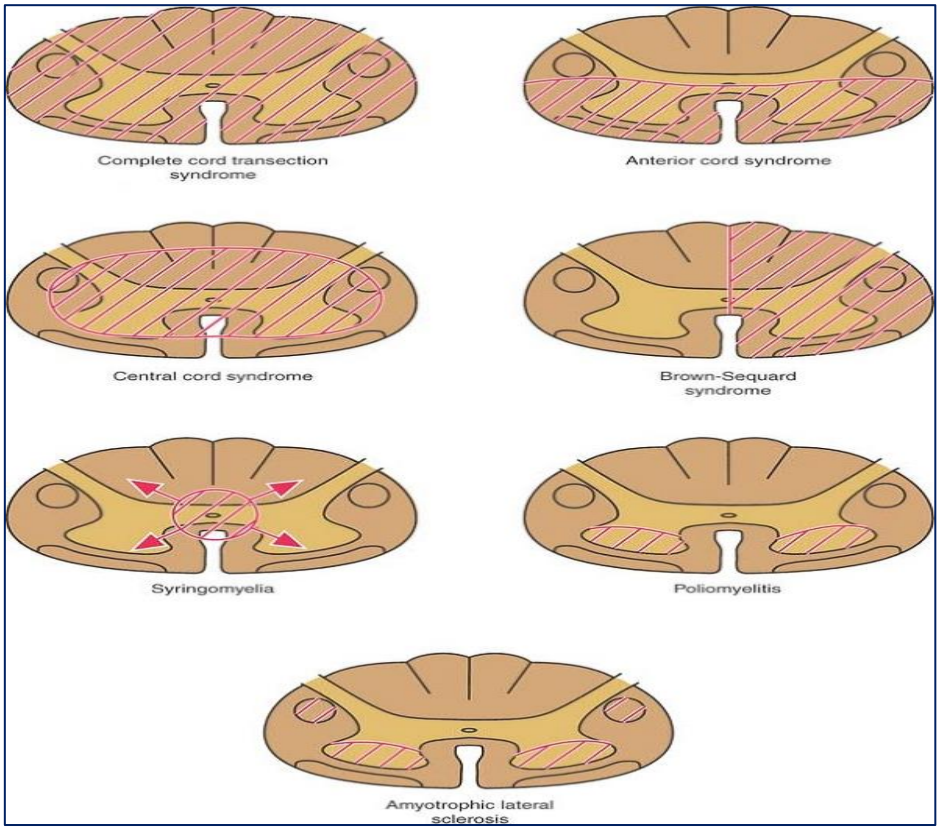
- signifies an injury of multiple lumbosacral nerve roots within the spinal canal distal to the termination of the spinal cord at L1-L2.
- Lower back pain, weakness and areflexia in the legs, saddle anesthesia, or loss of bladder function may occur.
- The problem must be distinguished from conus medullaris syndrome, acute transverse myelitis, and Guillain-Barré syndrome.
- Combined involvement of the conus medullaris and cauda equina can occur.
- CES is most commonly due to a large ruptured lumbosacral intervertebral disk, but other causes include lumbosacral spine fracture, hematoma within the spinal canal (sometimes following lumbar puncture in patients with coagulopathy), and tumor or other compressive mass lesions.
- Treatment is surgical decompression, sometimes on an urgent basis in an attempt to restore or preserve motor or sphincter function, or radiotherapy for metastatic tumors

Special Patterns of Spinal Cord Disease

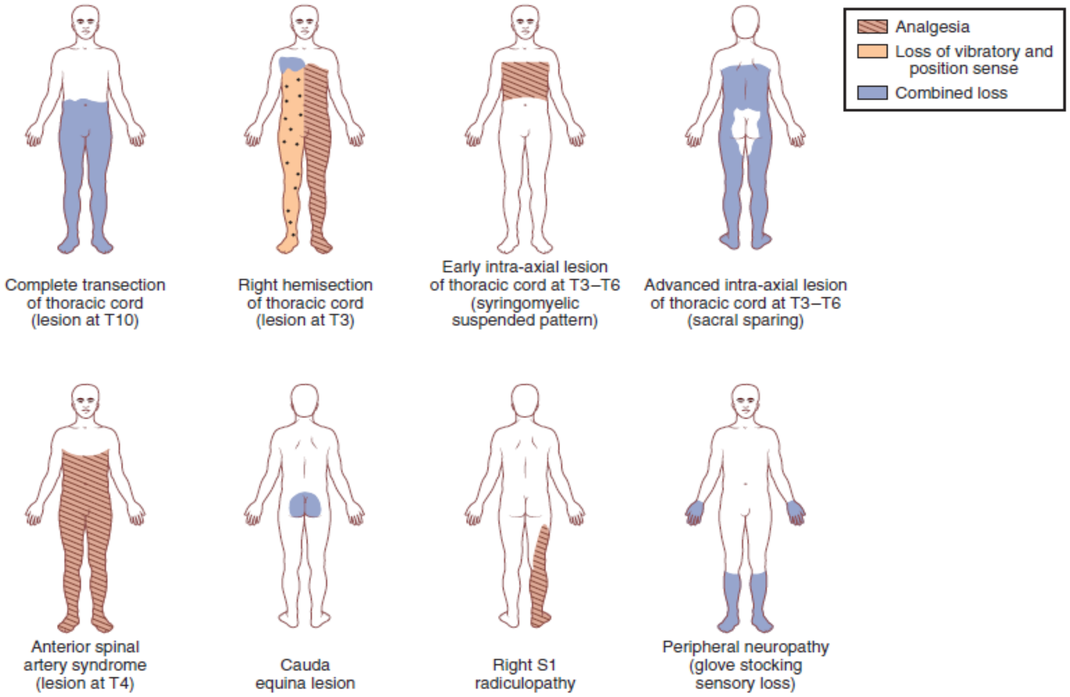

Posterior Columns
(Joint Position, Vibration, Pressure)
Fasciculus cuneatus
Fasciculus gracilis
C T L S
Dorsal root
Dorsal spinocerebellar tract
Ventral spinocerebellar tract
L S
Lateral spinothalamic tract
S L T C
Pain, temperature
Ventral root
Ventral spinothalamic tract
Pressure, touch (minor role)
Ventral (uncrossed) corticospinal tract
Distal limb movements (minor role)
Anterior horn (motor neurons)
Lateral corticospinal (pyramidal) tract
C T L S
Rubrospinal tract
Distal limb movements
P F E D
Lateral reticulospinal tract
Vestibulospinal tract
Ventral reticulospinal tract
Tectospinal tract
Axial and proximal limb movements

Figure; **Transverse section through the spinal cord,** composite representation, illustrating the principal ascending (*left*) and descending (*right*) pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated.

C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.


Complete cord transection syndrome
Anterior cord syndrome
Central cord syndrome
Brown-Sequard syndrome
Syringomyelia
Poliomyelitis
Amyotrophic lateral sclerosis

Picture; Common spinal cord syndromes


Analgesia
Loss of vibratory and position sense
Combined loss

Complete transection of thoracic cord (lesion at T10)

Right hemisection of thoracic cord (lesion at T3)

Early intra-axial lesion of thoracic cord at T3–T6 (syringomyelic suspended pattern)

Advanced intra-axial lesion of thoracic cord at T3–T6 (sacral sparing)

Anterior spinal artery syndrome (lesion at T4)

Cauda equina lesion

Right S1 radiculopathy

Peripheral neuropathy (glove stocking sensory loss)

Fig. 24.2 Characteristic sensory disturbances found in various spinal cord lesions in comparison with peripheral neuropathy.

- Most fiber tracts–including the posterior columns and the spinocerebellar and pyramidal tracts–are situated on the side of the body they innervate. However, afferent fibers mediating pain and temperature sensation ascend in the spinothalamic tract contralateral to the side they supply.
- The anatomic configurations of these tracts produce characteristic syndromes that provide clues to the underlying disease process.

Brown-Sequard [Hemicord] Syndrome

- This consists of **ipsilateral weakness** (corticospinal tract) **and loss of joint position and vibratory sense** (posterior column), **with contralateral loss of pain and temperature sense** (spinothalamic tract) one or two levels below the lesion.
- Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral.
- Partial forms are more common than the fully developed syndrome.

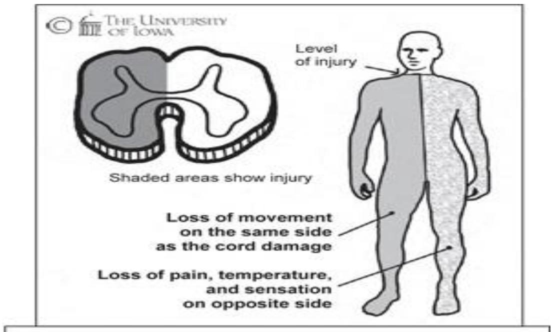

© The University of Iowa
Level of injury
Shaded areas show injury
Loss of movement on the same side as the cord damage
Loss of pain, temperature, and sensation on opposite side

Figure 12. Brown-Séquard Syndrome

Central Cord Syndrome

- This syndrome results from selective damage to the gray matter nerve cells and crossing spinothalamic tracts surrounding the central canal.
- In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a “dissociated” sensory loss, meaning loss of pain and temperature sensations over the shoulders, lower neck, and upper trunk (**cape distribution**), in contrast to preservation of light touch, joint position, and vibration sense in these regions.
- Spinal trauma, syringomyelia, and intrinsic cord tumors are the main causes.

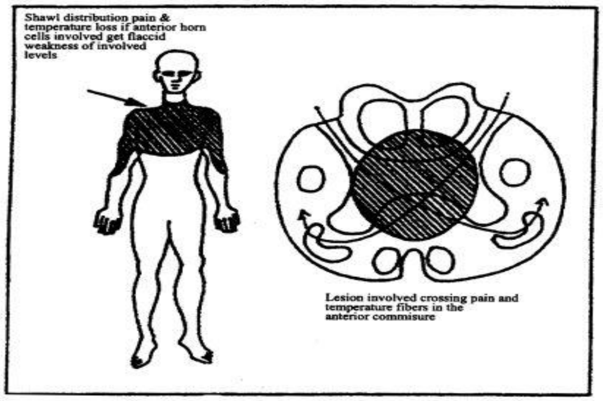
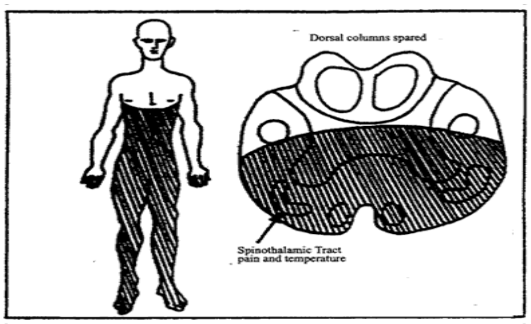

Shawl distribution pain & temperature loss if anterior horn cells involved get flaccid weakness of involved levels
Lesion involved crossing pain and temperature fibers in the anterior commisure

Figure 2-29: Central cord syndrome.

Anterior Spinal Artery Syndrome

- Infarction of the cord is generally the result of occlusion or diminished flow in this artery.
- The result is bilateral tissue destruction at several contiguous levels that spares the posterior columns.
- All spinal cord functions–motor, sensory, and autonomic–are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.


Dorsal columns spared
Spinothalamic Tract pain and temperature

Figure; Anterior Spinal Artery Syndrome

Foramen Magnum Syndrome

- Lesions in this area interrupt decussating pyramidal tract fibers destined for the legs, which cross caudal to those of the arms, resulting in weakness of the legs (*crural paresis*).
- Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm, an **"around the clock" pattern** that may begin in any of the four limbs.
- There is typically suboccipital pain spreading to the neck and shoulders.

Intramedullary and Extramedullary Syndromes

- It is useful to differentiate *intramedullary* processes, arising within the substance of the cord, from *extramedullary* ones that lie outside the cord and compress the spinal cord or its vascular supply.
- The differentiating features are only relative and serve as clinical guides.
- With **extramedullary lesions, radicular pain is often prominent,** and there is early sacral sensory loss and spastic weakness in the legs with incontinence due to the superficial location of the corresponding sensory and motor fibers in the spinothalamic and corticospinal tracts.
- Regarding extramedullary lesions, a further distinction is made between **extradural and intradural masses**, as the former are generally malignant and the latter benign (neurofibroma being a common cause). Consequently, a long duration of symptoms favors an intradural origin.
- **Intramedullary lesions tend to produce poorly localized burning pain** rather than radicular pain and to spare sensation in the perineal and sacral areas **("sacral sparing"),** reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later.

Complete cord transection

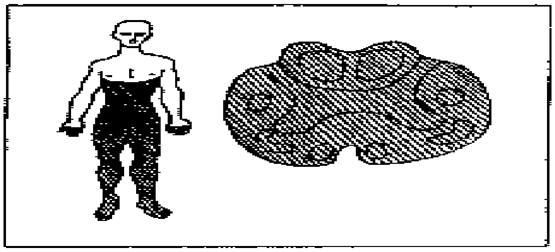


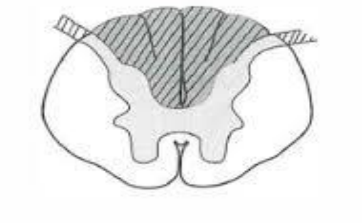
Figure 2-30: Complete spinal cord transection

- Causes
  - ✓ Trauma
  - ✓ Metastatic carcinoma
  - ✓ Multiple sclerosis
  - ✓ Spinal epidural haematoma
  - ✓ Autoimmune disorders
  - ✓ Post vaccinial syndromes
  - ✓ Infectious and postinfectious disorders
- All ascending tracts from below and descending tracts from above are interrupted
- Affects motor, sensory, and autonomic functions

- ✓ Sensory
    - all sensations are affected
    - Pin prick test is very valuable
    - Segmental paresthesia occurs at the level of lesion
- ✓ Motor
    - Paraplegia due to corticospinal tract
    - First spinal shock-followed by hypertonic hyper reflexic paraplegia
    - Loss of abdominal and cremasteric reflexes
    - At the level of lesion LMN signs occur
- ✓ Autonomic-
    - Urinary retention and constipation
    - Anhidrosis, trophic skin changes, vasomotor instability below the level of lesion
    - Sexual dysfunction can occur

Posterior column syndrome

- ➢ Occurs due to neurosyphilis, diabetes mellitus
- ➢ Usually occurs 10 to 20 yrs after infection
- ➢ Sensory
    - ✓ Impaired position and vibration sense in LL
    - ✓ Tactile and postural hallucinations can occur
    - ✓ Numbness or paresthesia are frequent complaints
    - ✓ Sensory ataxia
    - ✓ Positive rhomberg sign
- ➢ Corticospinal tracts are spared

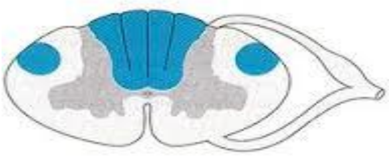


Figure; **Posterior column syndrome**

Posterolateral column disease

- Causes;
    - ✓ Vit B12 deficiency
    - ✓ AIDS
    - ✓ HTLV Associated myelopathy
    - ✓ Cervical spondylosis
- Affects both the dorsal column and the lateral corticospinal tracts
- Paresthesia in feet
- Loss of proprioception and vibration in legs
- Sensory ataxia
- positive rhomberg sign
- Bladder atony
- Corticospinal tract involvement
    - ✓ Spasticity

  - ✓ Hyperreflexia
  - ✓ Bilateral Babinski sign
- AIDS associated dementia and spastic bladder is present
- HTLV associated myelopathy
  - ✓ slowly progressive paraparesis
  - ✓ increase in csf igG antibodies to HTLV1



Figure; **Posterolateral column disease**

1.2.1 Acute and subacute spinal cord diseases

- Symptoms of the cord diseases that evolve over days or weeks are focal neck or back pain, followed by various combinations of paresthesia's, sensory loss, motor weakness, and sphincter disturbance.
- There may be mild sensory symptoms only or a devastating functional transection of the cord.
- When paresthesia's begin in the feet and then ascend a polyneuropathy is often considered, and in such cases the presence of bladder disturbances and a sharply demarcated spinal cord level provide important clues to the spinal cord origin of the disease.
- In severe and abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days or weeks; persistent areflexic paralysis with a sensory level usually indicates necrosis over multiple segments of the spinal cord.

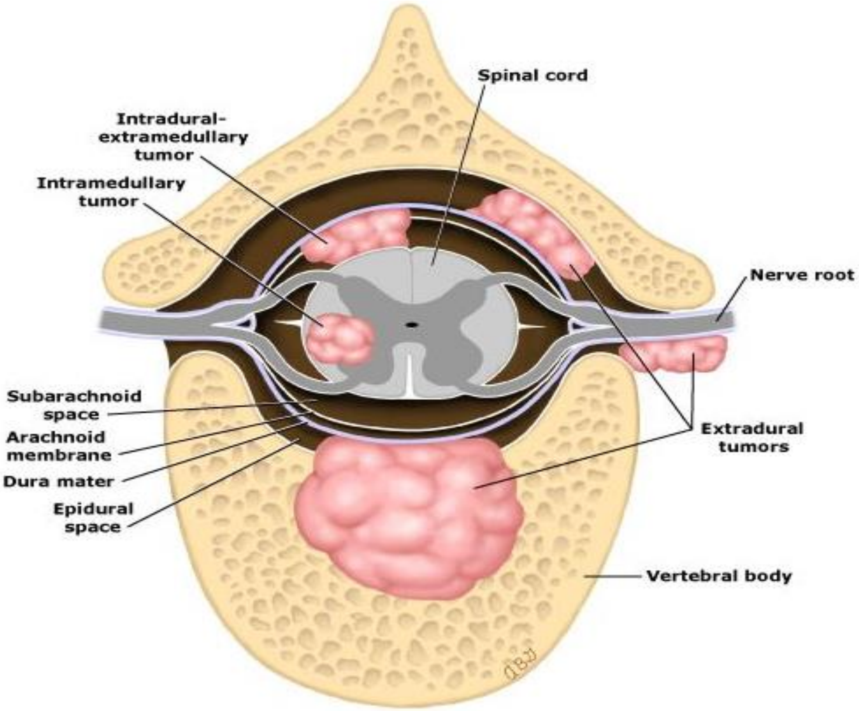
Distinguishing Compressive from No compressive Myelopathy

- The first priority is to exclude treatable compression of the cord by a mass lesion.
- The common causes are
  - ✓ Tumor
  - ✓ Epidural abscess or hematoma
  - ✓ Herniated disk, and
  - ✓ Spondylitic vertebral pathology.
- **Epidural compression** due to malignancy or abscess often causes **warning signs of neck or back pain, bladder disturbances, and sensory symptoms that precede the development of paralysis.**
- Spinal subluxation, hemorrhage, and **non-compressive etiologies** such as infarction are more likely to **produce myelopathy without antecedent symptoms**
- MRI with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure if it is available; it is often appropriate to image the entire spine (cervical through sacral regions) to search for additional clinically silent lesions.

- Once compressive lesions have been excluded, non-compressive causes of acute myelopathy that are intrinsic to the cord are considered, primarily vascular, inflammatory, and infectious etiologies.

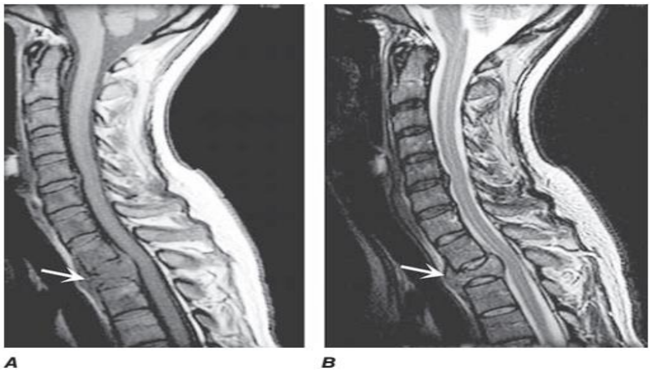
Compressive myelopathies

A. Neoplastic Spinal Cord Compression


Spinal cord
Intradural-extramedullary tumor
Intramedullary tumor
Nerve root
Subarachnoid space
Arachnoid membrane
Dura mater
Epidural space
Extradural tumors
Vertebral body

- In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent vertebral column.
- **Almost any malignant tumor can metastasize to the spinal column, with breast, lung, prostate, kidney, lymphoma, and myeloma being particularly frequent.**
- **The thoracic spinal column is most commonly involved**
  - ✓ Exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, probably from spread through Batson's plexus, a network of veins along the anterior epidural space.
- Retroperitoneal neoplasms (especially lymphomas or sarcomas) enter the spinal canal laterally through the intervertebral foramina and produce radicular pain with signs of weakness that corresponds to the level of involved nerve roots.
- **Pain is usually the initial symptom of spinal metastasis**
  - ✓ It may be aching and localized or sharp and radiating in quality and typically worsens with movement, coughing, or sneezing and characteristically awakens patients at night.

  - ✓ A recent onset of persistent back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis.
  - ✓ Rarely, pain is mild or absent.
- Plain radiographs of the spine and radionuclide bone scans have a limited role in diagnosis because they do not identify 15 - 20% of metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural space through the intervertebral foramina.
- **MRI** provides excellent anatomic resolution of the extent of spinal tumors and is able to distinguish between malignant lesions and other masses–epidural abscess, tuberculoma, lipoma, or epidural hemorrhage, among others–that present in a similar fashion.
  - ✓ Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI; after the administration of gadolinium, contrast enhancement may deceptively "normalize" the appearance of the tumor by increasing its intensity to that of normal bone marrow.



Figure; Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (*A*) and T2-weighted (*B*) magnetic resonance imaging scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in *A* signifies replacement by tumor.

- Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they often cross the disk space to involve the adjacent vertebral body.
- If there are radicular symptoms but no evidence of myelopathy, it may be safe to defer imaging for 24 - 48 h.
- Up to 40% of patients who present with cord compression at one level are found to have asymptomatic epidural metastases elsewhere; thus, imaging of the entire length of the spine is important to define the extent of disease.

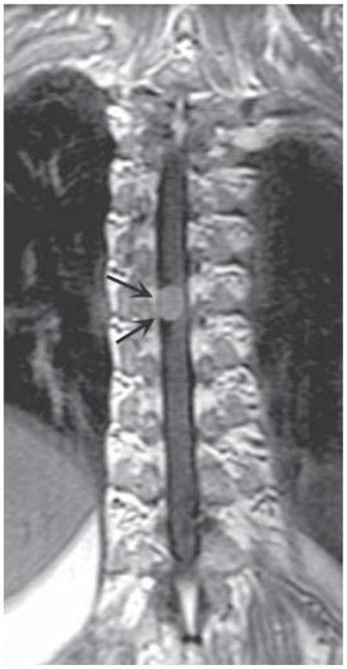
Treatment of Neoplastic Spinal Cord Compression

- Management of cord compression includes
  - ✓ Glucocorticoids to reduce cord edema
  - ✓ Local radiotherapy (initiated as early as possible) to the symptomatic lesion, and
  - ✓ Specific therapy for the underlying tumor type.
- Glucocorticoids

  - ✓ Glucocorticoids (typically **dexamethasone, 10 mg IV**, **stat**) can be administered before an imaging study if there is clinical suspicion of cord compression and continued at a lower dose (**4 mg, PO, QID**) until definitive treatment with radiotherapy and/or surgical decompression is completed.
- Radiotherapy
  - ✓ Radiotherapy alone may be effective even for some typically radioresistant metastases.
  - ✓ A good response to therapy can be expected in individuals who are ambulatory at presentation.
  - ✓ Treatment usually prevents new weakness, and some recovery of motor function occurs in up to one-third of patients.
  - ✓ Motor deficits (paraplegia or quadriplegia), once established for >12 h, do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.
  - ✓ Although most patients do not experience recurrences in the months following radiotherapy, with survival beyond 2 years recurrence becomes increasingly likely and can be managed with additional radiotherapy.
  - ✓ Biopsy of the epidural mass is unnecessary in patients with known primary cancer, but it is indicated if a history of underlying cancer is lacking.
- Surgery
  - ✓ Either decompression by laminectomy or vertebral body resection
  - ✓ Indicated when
    - ▪ signs of cord compression worsen despite radiotherapy
    - ▪ the maximum-tolerated dose of radiotherapy has been delivered previously to the site, or
    - ▪ a vertebral compression fracture or spinal instability contributes to cord compression.

Intradural mass

- In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign.
- **Meningiomas and neurofibromas** account for most of these, with occasional cases caused by chordoma, lipoma, dermoid, or sarcoma.
- **Meningiomas** are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal.

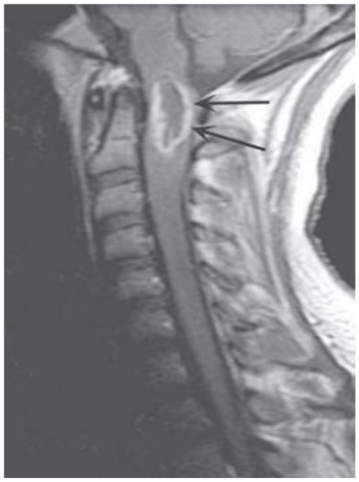


Figure; MRI of a thoracic meningioma. Coronal T1-weighted postcontrast image through the thoracic spinal cord demonstrates intense and uniform enhancement of a well-circumscribed extramedullary mass (*arrows*) that displaces the spinal cord to the left.

- **Neurofibromas** are benign tumors of the nerve sheath that typically arise from the posterior root; when multiple, neurofibromatosis is the likely etiology.
- Symptoms usually begin with radicular sensory symptoms followed by an asymmetric, progressive spinal cord syndrome.
- Therapy is surgical resection.

Primary intramedullary tumors of the spinal cord

- They are uncommon.
- They present as central cord or hemicord syndromes, often in the cervical region.
- There may be poorly localized burning pain in the extremities and sparing of sacral sensation.
- In adults, these lesions are ependymomas, hemangioblastomas, or low-grade astrocytomas.



Figure; **MRI of an intramedullary astrocytoma.** Sagittal T1-weighted postcontrast image through the cervical spine demonstrates expansion of the upper cervical spine by a mass lesion emanating from within the spinal cord at the corticomedullary junction. Irregular peripheral enhancement occurs within the mass (*arrows*).

- Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques.
- Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy and chemotherapy is uncertain.
- Secondary (metastatic) intramedullary tumors also occur, especially in patients with advanced metastatic disease, although these are not nearly as frequent as brain metastases.

Spinal Epidural Abscess

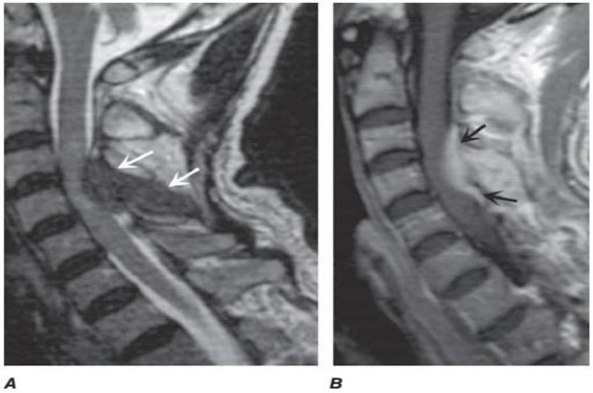
- Spinal epidural abscess presents with
  - ✓ **Midline back or neck pain**
  - ✓ **Fever, and**
  - ✓ **Progressive limb weakness.**
- Aching pain is almost always present, either over the spine or in a radicular pattern.
- **The duration of pain** prior to presentation is **generally ≤2 weeks** but may on occasion be several months or longer.
- **Fever is typically but not invariably present**, accompanied by **elevated WBC count, raised ESR and CRP**.
- As the abscess expands, further spinal cord damage results from venous congestion and thrombosis.
- **Once weakness and other signs of myelopathy appear, progression may be rapid and irreversible**.
- A more chronic sterile granulomatous form of abscess is also known, usually after treatment of an acute epidural infection.
- **Risk factors** include an
  - ✓ Impaired immune status (HIV, diabetes mellitus, renal failure, alcoholism, malignancy)
  - ✓ IV drug abuse, and
  - ✓ Infections of the skin or other tissues.
    - 2/3rd of epidural infections results from hematogenous spread of bacteria from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses; sinusitis), or deep viscera (bacterial endocarditis). The remainder arises from direct extension of a local infection to the subdural space
    - Examples of local predisposing conditions are
      - vertebral osteomyelitis
      - decubitus ulcers
      - lumbar puncture
      - epidural anesthesia, or
      - spinal surgery.
- **Etiology**
  - ✓ *S. aureus*

- MRSA is an important consideration, and therapy should be tailored to this possibility.

- ✓ gram-negative bacilli
- ✓ *Streptococcus*, anaerobes, and fungi can also cause epidural abscesses.
- ✓ **Tuberculosis from an adjacent vertebral source (Pott's disease) remains an important cause in the developing world.**

Investigations

- ➢ **MRI** localizes the abscess and excludes other causes of myelopathy.



Figure; **MRI of a spinal epidural abscess due to tuberculosis.** *A.* Sagittal T2-weighted free spin-echo MR sequence. A hypointense mass replaces the posterior elements of C3 and extends epidurally to compress the spinal cord (*arrows*). *B.* Sagittal T1-weighted image after contrast administration reveals a diffuse enhancement of the epidural process (*arrows*) with extension into the epidural space.

- ➢ **Blood cultures**
  - ✓ Are positive in > 50% of cases, but direct aspiration of the abscess at surgery is often required for a microbiologic diagnosis.
- ➢ **Lumbar puncture**
  - ✓ It Is **only** required if encephalopathy or other clinical signs raise the question of **associated meningitis**, a feature that is found in <25% of cases.
  - ✓ The level of the puncture should be planned to minimize the risk of meningitis due to passage of the needle through infected tissue.
  - ✓ A high cervical tap is sometimes the safest approach.
  - ✓ **CSF abnormalities** in epidural and subdural abscess consist of
    - **pleocytosis** with a preponderance of **polymorphonuclear cells**
    - an **elevated protein level**, and
    - a **reduced glucose levels**
  - ✓ the responsible organism is not cultured unless there is associated meningitis.

Treatment of Spinal Epidural Abscess

- ➢ Treatment is by **decompressive laminectomy with debridement combined with long-term antibiotic treatment.**

- Surgical evacuation prevents development of paralysis and may improve or reverse paralysis in evolution, but it is unlikely to improve deficits of more than several days in duration.
- **Broad-spectrum antibiotics** should be started empirically before surgery and then modified on the basis of culture results
  - ✓ vancomycin 15 - 20 mg/kg, IV, BID Plus
  - ✓ ceftriaxone, 1gm, IV, BID Plus
  - ✓ (if indicated for anaerobes) metronidazole 7.5 mg/kg IV, QID
- Medication is generally continued **for 6 - 8 weeks**.
- If surgery is contraindicated or if there is a fixed paraplegia or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, the choice of antibiotics may be guided by results of blood cultures.
- **Surgical management remains the treatment of choice unless the abscess is limited in size and causes few or no neurologic signs.**
- With prompt diagnosis and treatment of spinal epidural abscess, up to 2/3rd of patients experiences significant recovery.

Spinal Epidural Hematoma

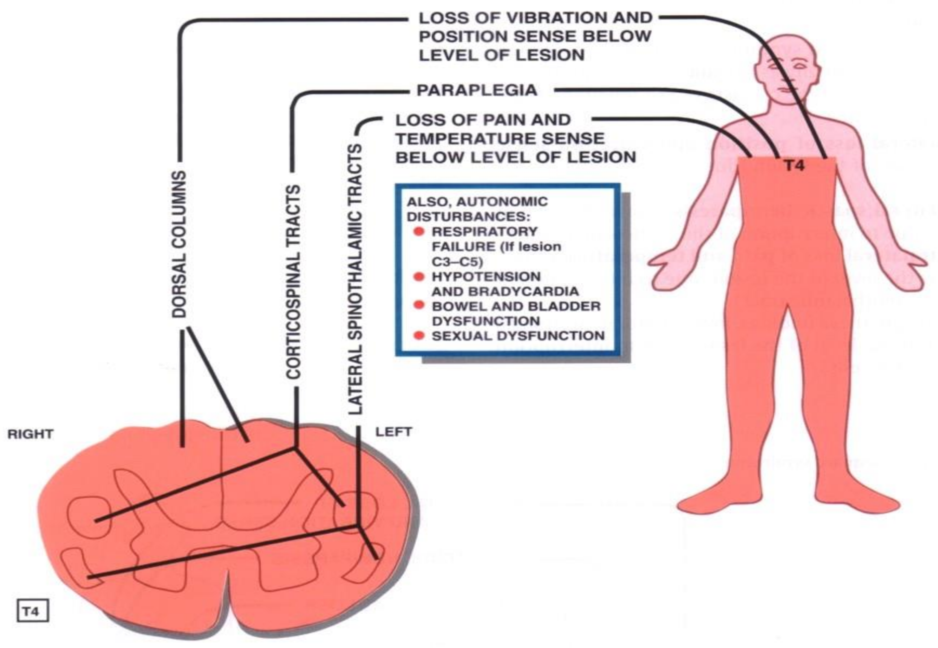
- Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder.
- Therapeutic anticoagulation, trauma, tumor, or blood dyscrasias are predisposing conditions.
- Rare cases complicate lumbar puncture or epidural anesthesia.
- MRI and CT confirm the clinical suspicion and can delineate the extent of the bleeding.
- Treatment consists of prompt reversal of any underlying clotting disorder and surgical decompression.
- Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively.
- Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with severe thrombocytopenia or other coagulopathies.

Hematomyelia

- Hemorrhage into the substance of the spinal cord is a rare result of trauma, intraparenchymal vascular malformation, vasculitis due to polyarteritis nodosa or SLE, bleeding disorders, or a spinal cord neoplasm.
- Hematomyelia presents as an acute painful transverse myelopathy.
- With large lesions, extension into the subarachnoid space results in subarachnoid hemorrhage.
- Diagnosis is by MRI or CT.
- Therapy is supportive, and surgical intervention is generally not useful.
  - ✓ An exception is hematomyelia due to an underlying vascular malformation, for which spinal angiography and endovascular occlusion may be indicated, or surgery to evacuate the clot and remove the underlying vascular lesion.

Non-Compressive myelopathies

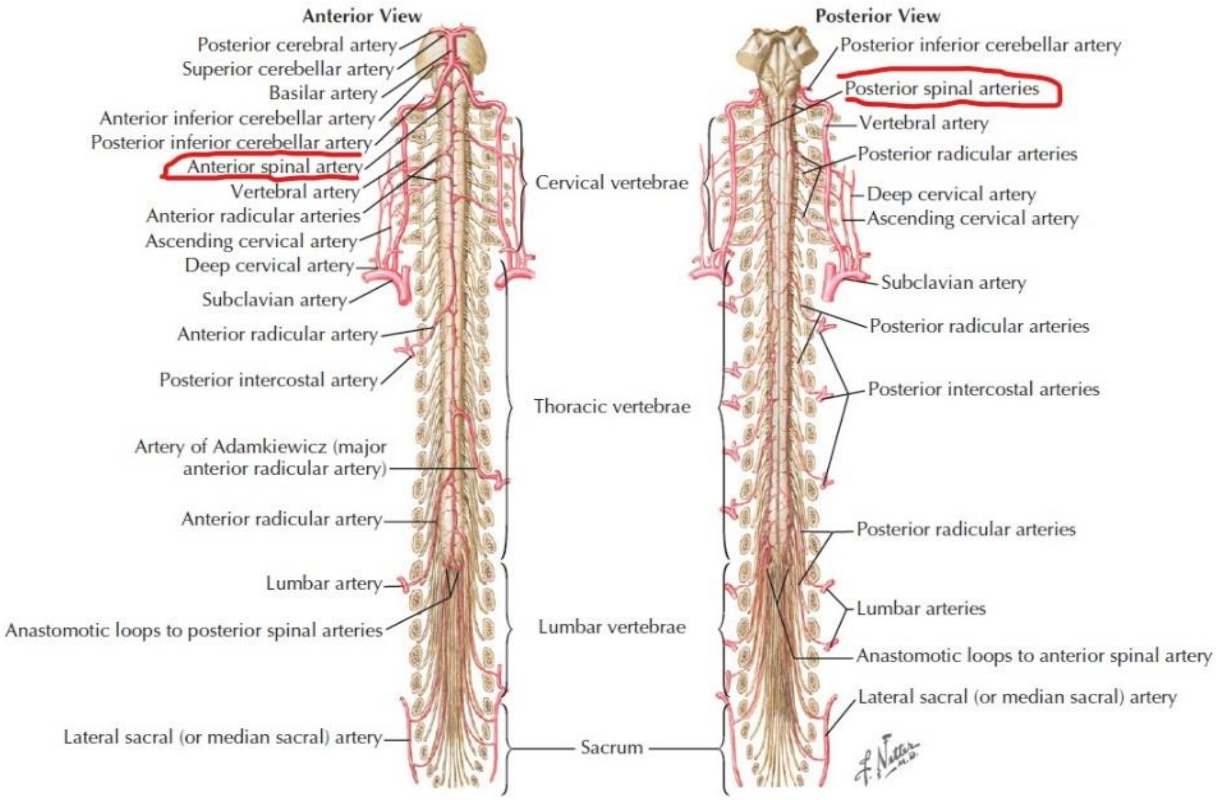
- The most frequent causes of non-compressive **acute transverse myelopathy** are;
    - ✓ spinal cord infarction
    - ✓ infectious (primarily viral) causes.
    - ✓ postinfectious or idiopathic transverse myelitis
        - which is presumed to be an immune condition related to acute disseminated encephalomyelitis
    - ✓ systemic inflammatory disorders, including SLE and sarcoidosis
    - ✓ demyelinating diseases, including multiple sclerosis (MS)
    - ✓ neuromyelitis optica (NMO)
- After spinal cord compression is excluded, the evaluation generally requires a lumbar puncture and a search for underlying systemic disease
- **Acute transverse myelopathies**
    - ✓ Rapidly progressive
    - ✓ Maximum deficit in hrs to days
    - ✓ The inflammation is generally restricted to one or two segments, usually in the thoracic cord
    - ✓ Symptoms develop rapidly over hrs; occasionally over several weeks
    - ✓ **Typically, the inflammation is bilateral, producing weakness and multimodality sensory disturbance below the level of the lesion**
    - ✓ Unilateral syndromes have been described as well
    - ✓ Almost all patients develop Leg weakness of varying severity, arm weakness if the lesion is in the cervical cord
    - ✓ Bowel and bladder dysfunction also occur
    - ✓ **Rapid onset complete paraplegia & spinal shock are associated with poorer outcomes**

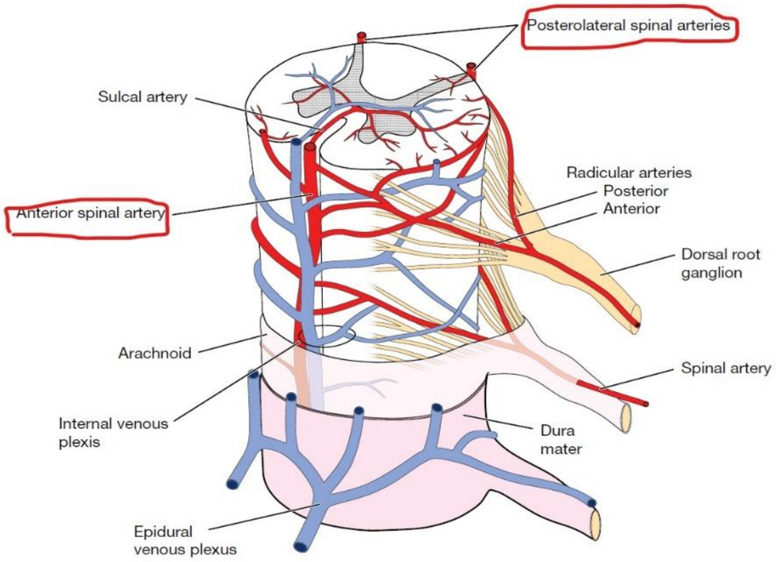

LOSS OF VIBRATION AND POSITION SENSE BELOW LEVEL OF LESION
PARAPLEGIA
LOSS OF PAIN AND TEMPERATURE SENSE BELOW LEVEL OF LESION
ALSO, AUTONOMIC DISTURBANCES:
RESPIRATORY FAILURE (If lesion C3–C5)
HYPOTENSION AND BRADYCARDIA
BOWEL AND BLADDER DYSFUNCTION
SEXUAL DYSFUNCTION
DORSAL COLUMNS
CORTICOSPINAL TRACTS
LATERAL SPINOTHALAMIC TRACTS
RIGHT
LEFT
T4
T4

Image; transverse myelopathy

☛ Spinal Cord Infarction

- The cord is supplied by three arteries that course vertically over its surface:
  - ✓ **a single anterior spinal artery** and
  - ✓ **paired posterior spinal arteries**.


Anterior View
Posterior cerebral artery
Superior cerebellar artery
Basilar artery
Anterior inferior cerebellar artery
Posterior inferior cerebellar artery
Anterior spinal artery
Vertebral artery
Anterior radicular arteries
Ascending cervical artery
Deep cervical artery
Subclavian artery
Anterior radicular artery
Posterior intercostal artery
Artery of Adamkiewicz (major anterior radicular artery)
Anterior radicular artery
Lumbar artery
Anastomotic loops to posterior spinal arteries
Lateral sacral (or median sacral) artery
Cervical vertebrae
Thoracic vertebrae
Lumbar vertebrae
Sacrum
Posterior View
Posterior inferior cerebellar artery
Posterior spinal arteries
Vertebral artery
Posterior radicular arteries
Deep cervical artery
Ascending cervical artery
Subclavian artery
Posterior radicular arteries
Posterior intercostal arteries
Posterior radicular arteries
Lumbar arteries
Anastomotic loops to anterior spinal artery
Lateral sacral (or median sacral) artery
F. Netter M.D.


Posterolateral spinal arteries
Sulcal artery
Radicular arteries
Posterior
Anterior
Anterior spinal artery
Dorsal root ganglion
Arachnoid
Spinal artery
Internal venous plexis
Dura mater
Epidural venous plexus

- The anterior spinal artery originates in paired branches of the vertebral arteries at the cranciocervical junction and is fed by additional radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11-L2 (artery of Adamkiewicz).
- At each spinal cord segment, paired penetrating vessels branch from the anterior spinal artery to supply the anterior two-thirds of the cord; the posterior spinal arteries, which often become less distinct below the midthoracic level, supply the posterior columns.
- Spinal cord ischemia can occur at any level; however, the presence of the artery of Adamkiewicz below, and the anterior spinal artery circulation above, creates a region of marginal blood flow in the upper thoracic segments.

- With hypotension or cross-clamping of the aorta, **cord infarction typically occurs at the level of T3-T4**, **and also at boundary zones between the anterior and posterior spinal artery territories**. The latter may result in a rapidly progressive syndrome over hours of weakness and spasticity with little sensory change.
- Acute infarction in the territory of the *anterior spinal artery* produces **“anterior cord syndrome”.**
  - ✓ Paraplegia or quadriplegia
  - ✓ Dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and
  - ✓ Loss of sphincter control
- **Onset may be sudden but more typically is progressive over minutes or a few hours,** unlike stroke in the cerebral hemispheres.
- **Sharp midline or radiating back pain** localized to the area of ischemia is frequent.
- **Areflexia** due to spinal shock is often present initially; **with time**, **hyperreflexia and spasticity appear**.
- Less common is infarction in the territory of the *posterior spinal arteries*, resulting in loss of posterior column function either on one side or bilaterally.
- **Causes** of spinal cord infarction include;
  - ✓ Aortic atherosclerosis
  - ✓ Dissecting aortic aneurysm
  - ✓ Vertebral artery occlusion or dissection in the neck
  - ✓ Aortic surgery
  - ✓ Profound hypotension from any cause.
  - ✓ A *surfer’s myelopathy*
  - ✓ Cardiogenic emboli
  - ✓ Vasculitis
  - ✓ collagen vascular disease (particularly SLE, Sjögren’s syndrome, and the antiphospholipid antibody syndrome).
  - ✓ In a substantial number of cases, **no cause can be found**, and thromboembolism in arterial feeders is suspected.
- **MRI may fail** to demonstrate infarctions of the cord, especially **in the first day**, but often the imaging becomes abnormal at the affected level.
- In cord infarction due to presumed thromboembolism, acute anticoagulation is not indicated, with the possible exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course.
- Prognosis following spinal cord infarction is influenced by the severity of the deficits at presentation; patients with severe motor weakness and those with persistent areflexia usually do poorly

2. Acute infectious myelitis (a.k.a Acute transverse myelitis)

- Many viruses have been associated with an acute myelitis that is infectious in nature rather than postinfectious.
- Nonetheless, the two processes are often difficult to distinguish.
- Etiologies
  - ✓ Viral → **most common**
    - Herpes zoster
    - HSV types 1 and 2

  - HSV-2 (and less commonly HSV-1) produces a distinctive syndrome of recurrent sacral cauda equina neuritis in association with outbreaks of genital herpes (Elsberg's syndrome).
  - EBV
  - CMV
  - rabies virus
  - Zika virus
  - Poliomyelitis → it is the prototypic viral myelitis, but it is more or less restricted to the anterior gray matter of the cord containing the spinal motoneurons.
  - Enteroviruses (including enterovirus 71 and coxsackie)
  - Japanese encephalitis and other flaviviruses such as West Nile virus.
  - Chronic viral myelitic infections, such as those due to HIV or HTLV-1
- ✓ Bacterial and mycobacterial myelitis (most are essentially abscesses) are less common than viral causes and much less frequent than cerebral bacterial abscess.
  - Almost any pathogenic species may be responsible, including
    - *Borrelia burgdorferi* (Lyme disease)
    - *Listeria monocytogenes*
    - *Mycobacterium tuberculosis,* and
    - *Treponema pallidum* (syphilis).
  - *Mycoplasma pneumoniae* may be a cause of myelitis, but its status is uncertain because many cases are more properly classified as postinfectious.
- ✓ Parasitic
  - Schistosomiasis is an important cause of parasitic myelitis in endemic areas.
    - The process is intensely inflammatory and granulomatous, caused by a local response to tissue-digesting enzymes from the ova of the parasite, typically *Schistosoma hematobium* or *Schistosoma mansoni*.
  - Toxoplasmosis can occasionally cause a focal myelopathy, and this diagnosis should especially be considered in patients with AIDS.
  - *Cysticercosis* is another consideration in pork meet users, although myelitis from this helminth is far less common than parenchymal brain or meningeal involvement.

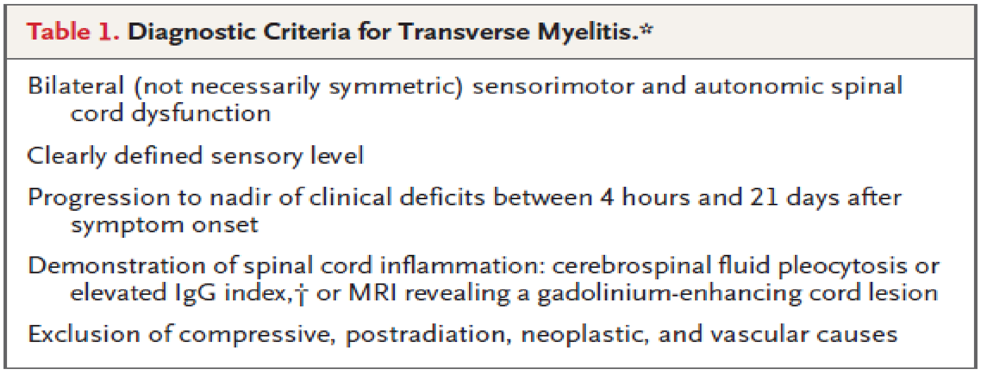


Table 1. Diagnostic Criteria for Transverse Myelitis.*

Bilateral (not necessarily symmetric) sensorimotor and autonomic spinal cord dysfunction
Clearly defined sensory level
Progression to nadir of clinical deficits between 4 hours and 21 days after symptom onset
Demonstration of spinal cord inflammation: cerebrospinal fluid pleocytosis or elevated IgG index,† or MRI revealing a gadolinium-enhancing cord lesion
Exclusion of compressive, postradiation, neoplastic, and vascular causes

* Clinical events that are consistent with transverse myelitis but that are not associated with cerebrospinal fluid abnormalities or abnormalities detected on MRI and that have no identifiable underlying cause are categorized as possible

idiopathic transverse myelitis.

† The IgG index is a measure of intrathecal synthesis of immunoglobulin and is calculated with the use of the following formula: (CSF IgG ÷ serum IgG) ÷ (CSF albumin ÷ serum albumin), where CSF denotes cerebrospinal fluid.

Management

- In cases of suspected viral myelitis, it may be appropriate to begin specific therapy pending laboratory confirmation.
- Herpes zoster, HSV, and EBV myelitis are treated with
  - ✓ Acyclovir,10 mg/kg, IV, TID for 10 - 14 days or
  - ✓ valacyclovir 2 g PO, TID for 10 - 14 days
- CMV is treated with
  - ✓ Ganciclovir, 5 mg/kg IV BID) for 2 weeks

    plus
  - ✓ Foscarnet, 60 mg/kg IV TID) for 2 weeks or
  - ✓ Cidofovir, 5 mg/kg per week for 2 weeks.

3. Postinfectious myelitis

- Many cases of myelitis, termed *postinfectious* or *postvaccinal*, follow an infection or vaccination.
- Numerous organisms have been implicated, including
  - ✓ EBV
  - ✓ CMV
  - ✓ Mycoplasma
  - ✓ Influenza
  - ✓ Measles
  - ✓ Varicella
  - ✓ mumps, and
  - ✓ yellow fever.
- As in the related disorder acute disseminated encephalomyelitis, postinfectious myelitis often begins as the patient appears to be recovering from an acute febrile infection, or in the subsequent days or weeks, but an infectious agent cannot be isolated from the nervous system or CSF.
- The presumption is that the myelitis represents an autoimmune disorder triggered by infection and is not due to direct infection of the spinal cord.
- Treatment is usually with glucocorticoids or, in fulminant cases, plasma exchange.

4. Multiple sclerosis (MS)

- **MS** may present with acute myelitis
- MS attacks rarely cause a transverse myelopathy (i.e., attacks of bilateral sensory disturbances, unilateral or bilateral weakness, and bladder or bowel symptoms), but it is among the most common causes of a partial cord syndrome.

- MRI findings in MS-associated myelitis typically consist of mild swelling of the cord and diffuse or multifocal “shoddy” areas of abnormal signal on T2-weighted sequences.
- Contrast enhancement, indicating disruption in the blood-brain barrier associated with inflammation, is present in many acute cases.
- Treatment of acute episodes of MS-associated myelitis consists of methylprednisolone (500 mg, IV daily for 3 days) followed by oral prednisone (1 mg/kg/d for several weeks, then gradual taper).
- A course of plasma exchange may be indicated for severe cases if glucocorticoids are ineffective.

1.2.2 Chronic myelopathies (spinal cord diseases)

1) Syringomyelia

- Syringomyelia is a developmental cavity of the cervical cord that may enlarge and produce progressive myelopathy or may remain asymptomatic.
- Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years.
- Many young patients acquire a cervical-thoracic scoliosis.
- More than half of all cases are associated with Chiari type 1 malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal.
- The presentation is **a central cord syndrome** consisting of a regional dissociated sensory loss (loss of pain and temperature sensation with sparing of touch and vibration) and areflexic weakness in the upper limbs.
- The sensory deficit has a distribution that is “suspended” over the nape of the neck, shoulders, and upper arms (**cape distribution**) or in the hands.
- Most cases begin asymmetrically with unilateral sensory loss in the hands that leads to injuries and burns that are not appreciated by the patient.
- Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes in the arms reflects expansion of the cavity in the gray matter of the cord.
- As the cavity enlarges and compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and a Horner’s syndrome appear.
- Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level or above).
- In cases with Chiari malformations, cough-induced headache and neck, arm, or facial pain may be reported.
- Extension of the syrinx into the medulla, syringobulbia, causes palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness or vertigo, and tongue weakness with atrophy.
- MRI accurately identifies developmental and acquired syrinx cavities and their associated spinal cord enlargement.

- Images of the brain and the entire spinal cord should be obtained to delineate the full longitudinal extent of the syrinx, assess posterior fossa structures for the Chiari malformation, and determine whether hydrocephalus is present.

Treatment of syringomyelia

- Treatment of syringomyelia is generally unsatisfactory.
- The Chiari tonsillar herniation may be decompressed, generally by suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft.
- With Chiari malformations, shunting of hydrocephalus generally precedes any attempt to correct the syrinx.
- Surgery may stabilize the neurologic deficit, and some patients improve.
- Patients with few symptoms and signs from the syrinx do not require surgery and are followed by serial clinical and imaging examinations.
- Syrinx cavities secondary to trauma or infection, if symptomatic, are treated with a decompression and drainage procedure in which a small shunt is inserted between the cavity and subarachnoid space; alternatively, the cavity can be fenestrated.
- Cases due to intramedullary spinal cord tumor are generally managed by resection of the tumor.

2) Subacute combined degeneration (Vit B12 deficiency)

- This treatable myelopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness.
- Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs is an important diagnostic clue.
- Optic atrophy and irritability or other cognitive changes may be prominent in advanced cases and are occasionally the presenting symptoms.
- The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg's sign.
- Causes include dietary deficiency, especially in vegans, and gastric malabsorption syndromes including pernicious anemia.
- The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B12 concentration, and elevated serum levels of homocysteine and methylmalonic acid.
- Treatment is by replacement therapy, beginning with 1000 μg of intramuscular vitamin B12 repeated at regular intervals or by subsequent oral treatment.

3) Tabes dorsalis

- The classic syphilitic syndromes of tabes dorsalis and meningovascular inflammation of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders.

- The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face.
- Ataxia of the legs and gait due to loss of position sense occurs in half of patients.
- Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15 - 30% of patients.
- **The cardinal signs of tabes are**
  - ✓ loss of reflexes in the legs
  - ✓ impaired position and vibratory sense
  - ✓ Romberg sign; and
  - ✓ in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate.
- Diabetic polyradiculopathy may simulate this condition.
- Treatment of tabes dorsalis and other forms of neurosyphilis consists of **penicillin G**, IV/IM in combination with oral probenecid

Reading Assignment

4) Chronic myelopathy of Multiple sclerosis
5) Spondylotic myelopathy
6) Vascular malformation of the cord and dura
7) Hereditary spastic paraplegia
8) Adeno myeloneuropathy
9) Hypocupric myelopathy

1.2.3 Rehabilitation of spinal cord disorders

- The prospects for recovery from an acute destructive spinal cord lesion fade after ~6 months.
- The disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete
- **Unexplained fever**, worsening of spasticity, or deterioration in neurologic function should prompt a search for infection, thrombophlebitis, or an intraabdominal pathology.
  - ✓ The loss of normal thermoregulation and inability to maintain normal body temperature can produce recurrent fever (*quadriplegic fever*), although **most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.**
- **Bladder dysfunction** generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature.
  - ✓ Detrusor spasticity is treated with anticholinergic drugs (oxybutynin, 2.5 - 5 mg qid) or TCA with anticholinergic properties **(imipramine, 25 - 200 mg/d**).

  - Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the α-adrenergic blocking agent **terazosin (1 - 2 mg TID or QID) Or Tamsulosin 0.4mg, PO, daily, with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter**.
  - Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit).
  - Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization.
- Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and **avoid colonic distention or obstruction**.
- Patients with acute cord injury are at risk for **venous thrombosis and pulmonary embolism**.
  - Use of **calf-compression devices and anticoagulation** with LMWH is recommended.
  - In cases of persistent paralysis, **anticoagulation should probably be continued for 3 months.**
- **Prophylaxis against decubitus ulcers** should involve
  - **Frequent changes in position** in a chair or bed
  - the use of special mattresses, and
  - **cushioning of areas where pressure sores often develop**, such as the sacral prominence and heels.
- **Early treatment of ulcers with careful cleansing**, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone
- Spasticity is aided by **stretching exercises** to maintain mobility of joints.
- **Diazepam is useful for leg spasms** that interrupt sleep (2 - 4 mg at bedtime).
- **Management of chronic pain**
  - Despite the loss of sensory function, many patients with spinal cord injury experience chronic pain sufficient to diminish their quality of life
- A paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6.
  - Headache, flushing, and diaphoresis above the level of the lesion, as well as hypertension with bradycardia or tachycardia, are the major symptoms.
  - The trigger is typically a noxious stimulus–for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer–below the level of the cord lesion.
  - Treatment consists of removal of offending stimuli or short-acting antihypertensive drugs are useful in some patients.
- Attention to these details allows longevity and a productive life for patients with complete transverse myelopathies.

1.3 GBS (Guillain-Barré syndrome)

- Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature.
- Males are at slightly higher risk for GBS than females, and in Western countries, adults are more frequently affected than children.

Clinical Manifestations

- 8 A's of GBS
  - ✓ **Autoimmune**
  - ✓ **Areflexia**
  - ✓ **Ascending paralysis**
  - ✓ **Acute**
  - ✓ **Afebrile**
  - ✓ **Absence of sensory level**
  - ✓ **Autonomic involvement → OHT, arrythmia**
  - ✓ **Acellular CSF** (albumin cytogenic dissociation → decreased number of cells but, increased protein/albumin of CSF)
- GBS manifests as a rapidly evolving **areflexic motor paralysis with or without sensory disturbance.**
- **The usual pattern is an ascending paralysis** that may be first noticed as rubbery legs.
- **Weakness typically Acute evolving over hours to a few days** and is frequently accompanied by tingling dysesthesias in the extremities.
- **The legs are usually more affected than the arms**, and facial diparesis is present in 50% of affected individuals.
- The lower cranial nerves are also frequently involved, causing bulbar weakness with difficulty handling secretions and maintaining an airway; the diagnosis in these patients may initially be mistaken for brainstem ischemia.
- Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in ~50% of patients.
- Most patients require hospitalization, and in different series, up to 30% require ventilatory assistance at some time during the illness.
- The need for mechanical ventilation is associated with more severe weakness on admission, a rapid tempo of progression, and the presence of facial and/or bulbar weakness during the first week of symptoms.
- **Fever and constitutional symptoms are absent** at the onset and, if present, cast doubt on the diagnosis.
- Deep tendon reflexes attenuate or disappear within the first few days of onset.
- Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected.
- Bladder dysfunction may occur in severe cases but is usually transient.
- If bladder dysfunction is a prominent feature and comes early in the course or **there is a sensory level on examination, diagnostic possibilities other than GBS should be considered, particularly spinal cord disease**.
- Once clinical worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely.
- **Autonomic involvement is common** and may occur even in patients whose GBS is otherwise mild.
  - ✓ The usual manifestations are loss of vasomotor control with wide fluctuations in blood pressure, postural hypotension, and cardiac dysrhythmias.
  - ✓ These features require close monitoring, and management and can be fatal.
- **Pain is another common feature of GBS**

- ✓ in addition to the acute pain described above, a deep aching pain may be present in weakened muscles that patients liken to having over exercised the previous day.
- ✓ Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement.
- ✓ These pains are self-limited and often respond to standard analgesics.

Subtypes of GBS

- ➢ Several subtypes of GBS are recognized, as determined primarily by electrodiagnostic (Edx) and pathologic distinctions (see table below).
  - ✓ **Acute inflammatory demyelinating polyneuropathy (AIDP) → The most common variant**
  - ✓ **Acute motor axonal neuropathy (AMAN)**
  - ✓ **Acute motor sensory axonal neuropathy (AMSAN).**
  - ✓ **Miller Fisher syndrome (MFS)**
    - ▪ regional variant which presents as **rapidly evolving ataxia and areflexia** of limbs without weakness**, and ophthalmoplegia,** often with **pupillary paralysis.**
    - ▪ The MFS variant accounts for ~5% of all cases
  - ✓ Other regional variants of GBS include
    - ▪ Pure sensory forms
    - ▪ ophthalmoplegia as part of severe motor-sensory GBS
    - ▪ GBS with severe bulbar and facial paralysis, sometimes associated with antecedent CMV infection and
    - ▪ acute pandysautonomia

axonal variants, which are often clinically severe

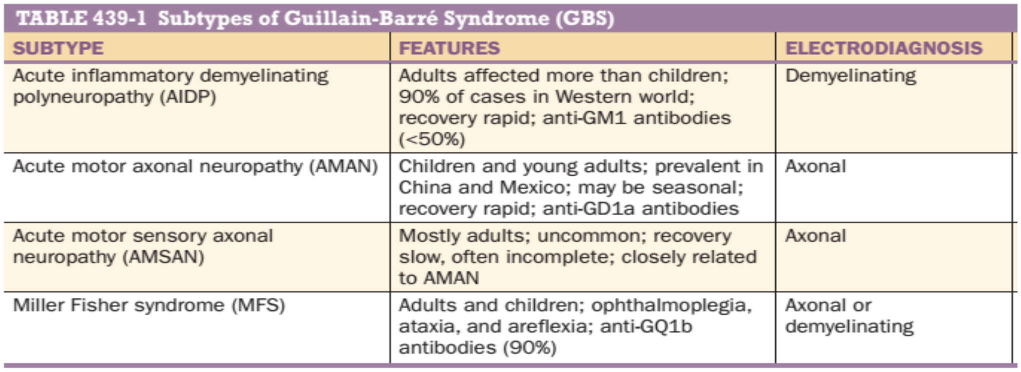


TABLE 439-1 Subtypes of Guillain-Barré Syndrome (GBS)

SUBTYPE	FEATURES	ELECTRODIAGNOSIS
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal
Miller Fisher syndrome (MFS)	Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Axonal or demyelinating

Antecedent Events

- Approximately 70% of cases of GBS occur 1 - 3 weeks after an acute infectious process, usually respiratory or GI.
- 20 - 30% of all cases are preceded by infection or reinfection with *Campylobacter jejuni*.
- A similar proportion is preceded by CMV or EBV.
- Other viruses (e.g., HIV, hepatitis E, Zika) and also *Mycoplasma pneumoniae* have been identified as agents involved in antecedent infections, as have recent immunizations.

- Post vaccine association → influenza vaccine, Older-type rabies vaccine
- GBS also occurs more frequently in patients with lymphoma (including Hodgkin's disease), in HIV-seropositive individuals, and in patients with SLE.

Laboratory Features

- CSF findings are distinctive, consisting of an **elevated CSF protein level (100 - 1000 mg/dL]) without accompanying pleocytosis.**
- The CSF is often normal when symptoms have been present for ≤48 h; by the end of the first week, the level of protein is usually elevated.
- A transient increase in the CSF white cell count (10 - 100/μL) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection, leukemia or lymphoma with infiltration of nerves, or neurosarcoidosis.
- Electrodiagnostic studies

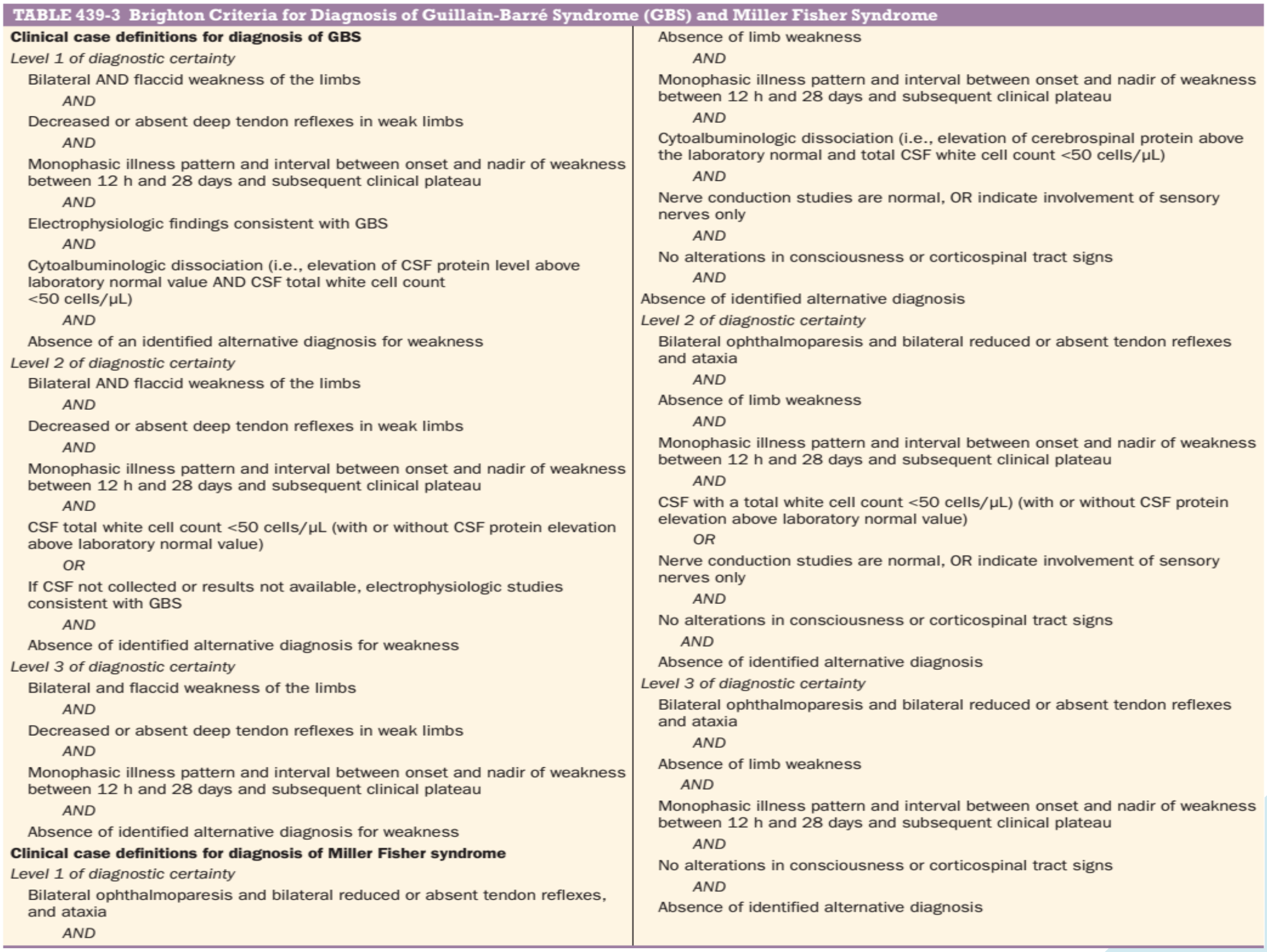


TABLE 439-3 Brighton Criteria for Diagnosis of Guillain-Barré Syndrome (GBS) and Miller Fisher Syndrome

Clinical case definitions for diagnosis of GBS

Level 1 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Electrophysiologic findings consistent with GBS
AND
Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μL)
AND
Absence of an identified alternative diagnosis for weakness

Level 2 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
CSF total white cell count <50 cells/μL (with or without CSF protein elevation above laboratory normal value)
OR
If CSF not collected or results not available, electrophysiologic studies consistent with GBS
AND
Absence of identified alternative diagnosis for weakness

Level 3 of diagnostic certainty

Bilateral and flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Absence of identified alternative diagnosis for weakness

Clinical case definitions for diagnosis of Miller Fisher syndrome

Level 1 of diagnostic certainty

Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes, and ataxia
AND
Absence of limb weakness
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal and total CSF white cell count <50 cells/μL)
AND
Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis

Level 2 of diagnostic certainty

Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND
Absence of limb weakness
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
CSF with a total white cell count <50 cells/μL) (with or without CSF protein elevation above laboratory normal value)
OR
Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis

Level 3 of diagnostic certainty

Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND
Absence of limb weakness
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis

Treatment of GBS

- In the vast majority of patients with GBS, treatment should be initiated as soon after diagnosis as possible.
- Each day counts; ~2 weeks after the first motor symptoms, it is not known whether immunotherapy is still effective.
- If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility that an immunologic attack is still ongoing.
- **Either high-dose intravenous immune globulin (IVIg) or plasmapheresis** can be initiated, as they are equally effective for typical GBS.
- A combination of the two therapies is not significantly better than either alone.
- IVIg is often the initial therapy chosen because of its ease of administration and good safety record.
- IVIg may be preferable to plasma exchange (PE) for the AMAN and MFS variants of GBS.
- **IVIg is administered as five daily infusions for a total dose of 2 g/kg**.
- **A course of plasmapheresis usually consists of ~40—50 mL/kg PE 4 - 5 times over 7 - 10 days.**
- treatment reduces the need for mechanical ventilation by nearly half (from 27 to 14% with PE) and increases the likelihood of full recovery at 1 year (from 55 to 68%).
- Functionally significant improvement may occur toward the end of the first week of treatment or may be delayed for several weeks.
- The lack of noticeable improvement following a course of IVIg or PE is not an indication to treat with the alternate treatment.
- However, there are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month.
- Brief retreatment with the original therapy is usually effective in such cases.
- **Glucocorticoids have not been found to be effective in GBS.**
- Occasional patients with **very mild forms of GBS**, especially those who appear to have already reached a plateau when initially seen, **may be managed conservatively** without IVIg or PE.
- **In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep-vein thrombosis prophylaxis, cardiovascular status, early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy.**
- As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer).
- **Frequent turning and assiduous skin care** are important, as are **daily range-of motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.**

Prognosis and Recovery

- **Approximately 85**% of patients with **GBS achieve a full functional recovery within several months to a year**, although minor findings on examination (such as areflexia) may persist and patients often complain of continued symptoms, including fatigue.
- The mortality rate is <5% in optimal settings; **death usually results from secondary pulmonary complications.**
- Poor prognosis features

  - ✓ patients with severe proximal motor and sensory axonal damage.
  - ✓ advanced age
  - ✓ a fulminant or severe attack, and
  - ✓ a delay in the onset of treatment.
- Between 5 and 10% of patients with typical GBS have one or more late relapses; many of these cases are then classified as chronic inflammatory demyelinating polyneuropathy (CIDP).

Chronic inflammatory demyelinating polyneuropathy (CIDP)

- CIDP is distinguished from GBS by its chronic course.
- Onset is usually gradual over a few months or longer, but in a few cases, the initial attack is indistinguishable from that of GBS.
- In other respects, this neuropathy shares many features with the common demyelinating form of GBS, including elevated CSF protein levels and the Edx findings of acquired demyelination.
- Most cases occur in adults, and males are affected slightly more often than females.
- The incidence of CIDP is lower than that of GBS, but due to the protracted course, the prevalence is greater.

1.4 ALS (Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases)

- ALS is the most common progressive motor neuron disease.
- It is a prime example of a neurodegenerative disease and is arguably **the most devastating of the neurodegenerative disorders that produces progressive weakness, usually with mixed UMN & LMN signs**.
- The pathologic hallmark of motor neuron degenerative disorders is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons)
- Symptoms begin insidiously in older adults (usually >60 yrs) and progress inexorably
- In typical pts, there is asymmetric limb weakness with a mixture of UMN & LMN features
- Sensory & sphincter disturbances are usually absent
- MRI is normal
- EMG typically shows denervation in clinically affected muscles.
- Unusual variants of ALS… Primary Lateral Sclerosis

Chapter 8; Meningitis (ማጅራት ገትር)

Dr. Mulualem. G, Dr. Robel. D

Clinical features and how to write hx of meningitis patient

History

- Pt's may present with
    - Headache
    - Neck stiffness
    - Vomiting
- **Triads of meningitis** include **fever, headache and neck stiffness** → triads happen in 44% of pts
- 2 of 4 (fever, headache, stiff neck, change in Mentation) present in 95%
- **Fever and either headache, stiff neck or an altered level of consciousness will be present in nearly every patient**
    - >75% of patients have a decreased level of consciousness which ranges from lethargy to coma
- Seizure Occur in 20-40% as initial presentation or during the course of the illness
    - Focal seizures are usually due to
        - Structural causes
        - Focal arterial ischemia or infarction,
        - Cortical venous thrombosis with haemorrhage, or
        - Focal edema
    - Generalized seizure and status epilepticus may be due to
        - Hyponatremia,
        - Cerebral anoxia, or
        - Toxic effects of antimicrobials such as high dose penicillin
- Presentation may be *atypical* (eg, lethargy without fever) in the elderly and immunosuppressed.

Patient history characterization

- Headache
    - Gradual in onset
    - Intermittent / persistent
    - Globalized
    - Dull aching type
    - Severe/moderate
    - Aggravated by coughing, sitting position, loud voice
    - Relieved by sleeping and keeping silent
        - ✓ Worse during awakening from sleep

  - Occurs ''X'' times per month and lasts for ''Y'' minutes
  - May/may not be responsive to analgesics
- Neck stiffness
- Fever
  - Low grade *(in viral, fungal and TB meningitis)* or high grade *(in pyogenic/bacterial meningitis)*
  - Intermittent / persistent
  - Associated with chills and rigor. In most cases (especially in viral fungal and TB meningitis) there may not be chills or rigor
- Vomiting
  - Projectile (if there is increased ICP), if vomiting is projectile there is no preceding nausea i.e. projectile doesn't merely mean project forward
- Photophobia
- Associated with Abnormal body movement
  - Starts abruptly
  - With or without warning manifestations
  - Generalized/partial
  - With up rolling of the eyes and drooling of saliva
  - Followed by excessive salivation, bleeding from the tongue (tongue bite), urinary or faecal incontinence (observed by one of family members)
  - Finally, LOC → ask duration of LOC which is mostly less than 5 minutes
- Night sweat
- Weight loss

Common in TB meningitis

Risk factors

- URTI (sinusitis, otitis media → S.pneumonia)
- Pyogenic chest infection
- Pyogenic Dental infection → also high risk for brain abscess
- Chronic alcohol intake → S.pneumonia, N.meningitidis, brain abscess
- DM → S.pneumonia
- Immunocompromising condition → S.pneumonia, N.meningitidis
  - Old age
  - Malignancy (especially hematologic malignancy)
  - Malnutrition
  - Steroid use
  - Chemoradiotherapy
  - Chronic medical disease like RVI, DM, CLD, CKD…
  - Pregnancy
  - Splenectomy
    - ✓ RF for infection by encapsulated microorganisms like S.pneumonia

- Overcrowding (dormitory life, refuges, military camp) → meningococcal infection through nasal droplets, viral meningoencephalitis
- Skin or oral lesions → viral meningoencephalitis
- Geographic location
    - The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa known as **Meningitis belt** which stretches from Senegal in the west to Ethiopia in the east (26 countries)
    - North western part of Ethiopia is in the area of meningitis belt (Gondar, quara, metema, armachiho, metekel….)

Complication of meningitis

Acute complications	Chronic complications
Raised ICP Seizure Brain abscess DIC → especially in meningococcal infection Cerebral oedema Coma DHN Respiratory arrest Pericardial effusion	Hearing loss and blindness epilepsy Cognitive impairment Focal paralysis Subdural effusion Hydrocephalus Ataxia Bilateral adrenal haemorrhage

Sample history

Chief compliant

headache of one week duration

HPI

This patient was last relatively healthy a week back, at which time she began to experience a gradual onset of globalized, dull aching, persistent type of headache which is moderate in intensity, aggravated by coughing, sitting position and loud voice, relieved by sleeping and keeping silent associated with high grade intermittent fever with chills and rigors.

Two days before admission the headache got worsen and developed painful neck stiffness associated with 3 episodes of non-projectile, nonfoul smelling, non-blood tingled vomiting of ingested matter but no photophobia. She also developed 2 episodes of generalized abnormal body movements which Starts abruptly without warning manifestations, with up rolling of eyes, bleeding from tongue followed by excessive salivation and urinary incontinence which is observed by her brother. Finally, she loses her consciousness and gains her consciousness approximately 5 to 10 minutes later in each episode.

She neither visit any health facility nor took any antipain or antibiotics. Finally, her families bring her to our hospital when she develops abnormal body movement.

- No hx of discharge from the nose, ear, upper facial pain, ear/nose pain, morning frontal headache or rhinorrhea *(URTI → RF)*
- No hx of smoking or chronic alcohol intake *(RF)*
- No hx of cough, chest pain or contact with a known TB patient (meningitis from respiratory source like TB meningitis, bacterial meningitis /S.pneumonia, H.influenza/)
- No hx of skin rash, joint pain *(skin lesions like vesicles are RF for viral meningitis and petechae suggest meningococcal infection)*
- No hx of abdominal surgery *(splenectomy → RF)*
- No hx of DM, HTN or Asthma *(Chronic medical condition and immunocompromisation → RF)*
- She was not screened for RVI but no history of MSP, chronic diarrhea, oral thrush or body rash *(immunocompromisation → RF)*
- No hx of blindness or hearing difficulty *(chronic CXN)*
- No hx of gum bleeding, epistaxis, or bleeding from other sites *(DIC → CXN)*
- No hx of head trauma or neuro surgery *(RF for brain abscess, SAH → DDX)*
- No hx of swelling over the neck, axilla or groin *(carcinomatous meningitis → DDX)*
- No hx of MSP, penile or vaginal discharge *(syphilitic meningitis → DDX)*
- Lives in malaria non endemic area and no hx of malarial attack or travel hx to malaria endemic area *(cerebral mmalaria → DDX)*
- No family hx of similar illness *(migraine → DDX)*
- No hx of drug intake *(NSAIDS, antiepileptics, steroids → cause headache and neck stiffness → DDX, Steroids are immunosuppressive as RF, if empirical antibiotics was given it is better to consider partially treated meningitis)*

Finally, she was admitted to our hospital supported physically by her families

Physical examination (pertinent findings)

1 GA

2 Vital signs

- Cushing triad from raised ICP
    1. BP → HTN
    2. PR → bradycardia
    3. RR → irregular breathing pattern

3 HEENT

- Ear/nose tenderness, ear discharge, rhinorrhea (sinusitis, otitis media → RF)
- A history of **head trauma** with or without skull fracture or presence of a **chronically draining ear** is associated with **pneumococcal** involvement.
- Funduscopic findings: papilledema, absent venous pulsations

4 LGS

- Parotid enlargement → mumps

5 RS

6 CVS

7 Abdominal examination

8 GUS

9 MSS

10 IS

- Skin rash: Erythematous maculopapular, petechial, or purpuric over the trunk, LL, conjunctiva or mucous membrane (typical for meningococcal, may present with H. influenza and rare with pneumococcal)
- Grouped vesicles → VZV

NS

- **+ve Meningeal irritation signs** (Kerning sign, Brudzinski sign, Neck stiffness)
    - **Nuchal rigidity** (Sensitivity 30%)
    - **Kernig's sign** → Patient supine, hip flexed at 90, knee flexed at 90; +ve if passive extension of knee results in resistance
    - **Brudzinski's sign** → Patient supine and limbs supine; +ve if passive neck flexion if followed by involuntary hip and/or knee flexion.

- Kernig's and Brudzinski's signs are +ve in only 5% of Pts, but will be very specific for meningeal irritation if present.
- May be negative in
    - ✓ Very young or elderly patients
    - ✓ Immunocompromised
    - ✓ Severe coma
    - ✓ Partially treated meningitis
- Some patients may have focal neurologic findings (about 30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- Raised ICP signs
    - ✓ Change in mentation is the earliest sign
    - ✓ Papilledema
    - ✓ Dilated and poorly reactive pupil which indicate CN III palsy
    - ✓ CN VI palsy
    - ✓ Decerebrate posture
    - ✓ *Cushing reflex (bradycardia, hypertension, and irregular respirations).*

- Altered level of consciousness → viral meningoencephalitis
- Aphasia, ataxia, seizure → viral meningoencephalitis (seizure happens in bacterial meningitis also)

DDX

1. Meningitis
    - Pyogenic meningitis → i.e. bacterial meningitis
    - Viral (aseptic) meningitis
    - TB meningitis
        - ✓ Phases of TB
            - ☛ Prodromal phase → nonspecific smx like fever, night sweat, weight loss…
            - ☛ Meningitis phase → nuchal rigidity, CN palsy (single CN involved)
            - ☛ Coma (paralysis) → weakness, multiple CN involvement
    - Fungal meningitis
    - Chemical meningitis → also aseptic like viral
    - Syphilitic meningitis → meningitis occur in all stages of syphilis
    - Carcinomatous meningitis
        - ✓ Cmnly from ALL, AML, Lymphoma
        - ✓ Initially manifest with cmn C/F of leukaemia (bone pain, BM failure smx) then progress to meningitis
2. Cerebral malaria
    - Acute CXN of malaria
    - Infection with P. falciparum
    - Have nuchal rigidity, fever and headache
    - Cmn in endemic area
    - In repeated malarial attack if the last attack is ≥ 10 years, no risk of cerebral malaria (i.e. for cerebral malaria the last attack should be < 10 years)
    - LOC for > 30 minutes
        - ✓ Repeated seizure without gaining consciousness
        - ✓ Cerebral malaria is unlikely in fully awake patients
3. Brain abscess
    - Triads of brain abscess include fever, headache, FND
    - Rupture of the abscess is the cause of meningeal irritation
4. Typhoidal meningitis
    - Rare
    - Have psychotic features
    - 1st manifest as
        - ✓ Abdominal pain
        - ✓ Diarrhoea
        - ✓ Stepladder fever
        - ✓ Headache
        - ✓ prostration
        - ✓ It needs at least weeks to develop meningitis

   - Cmn in poor socioeconomic status
5. SAH
   - ''The worst headache ever''
   - The preceding mild to moderate headache caused by vascular aneurysm
   - Change in mentation
   - FND (e.g. Stroke)
6. Epidural or subdural empyema
7. Encephalitis → have associated bizarre behaviour and confusion
8. Vasculitis in cranium → thrombophlebitis (giant cell arthritis)
9. Migraine

IX

N.B.
High index of clinical suspicion is very important for early diagnosis of meningitis to avoid death or unfavorable complications.

- **LP (CSF Analysis)** → refer short case of nitsibin (click here → CSF analysis)
    - If LP is delayed (e.g after CT scan) or not indicated (uncontrolled significant bleeding tendencies), **withdraw two sets of blood culture prior to antibiotics**. Repeated (follow-up) LP is important if poor clinical response after 48hrs of appropriate antibiotic, or CSF shunt present, otherwise may not be necessary.
- **Blood cultures *before antibiotics are administered.*** Initial blood tests should include two sets of blood cultures.
    - Culture can be done also from CSF, throat swab, stool, urine based on aetiology
    - +ve for HiB, S.pneumonia, N.mengitidis
- CBC
    - Neutrophilic dominant leucocytosis in pyogenic meningitis
    - Leucocytosis also expected in brain abscess
- PICT
- Serum electrolyte
- OFT → RFT, LFT
- ESR & CRP
- PT & PTT → to r/o DIC
- Head CT
    - to rule out mass effect before LP (To r/o space occupying lesions if raised ICP is suspected and LP is contra indicated)

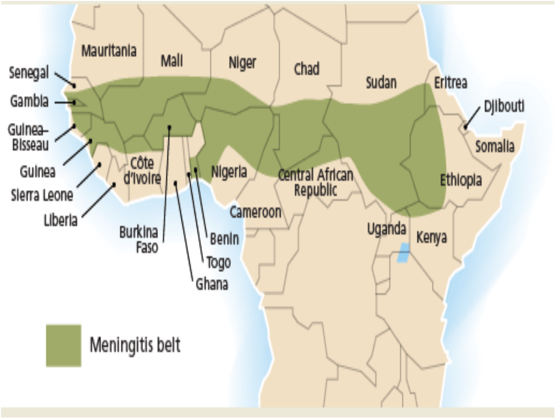
    - however, in patients with mass effect, herniation may occur without LP and may not occur even with LP
  - CT scan before LP in those with high-risk feature
    - ✓ age>60 year
    - ✓ immunosuppressed
    - ✓ history of CNS disease,
    - ✓ new-onset seizure
    - ✓ change in mental state
    - ✓ focal neurologic findings
    - ✓ papilledema
  - CT Can identify
    - ✓ CNS tumor
    - ✓ SAH
    - ✓ EDH/SDH
- MRI
  - Superior than CT to demonstrate cerebral edema and ischaemia
  - Can show diffuse meningeal enhancement
  - R/o space occupying lesions
- CXR
  - To identify the source of infection with cmn etiologies affecting chest and meninges like bacterial meningitis (S.pneumonia, H.influenza), TB meningitis
- PCR
  - For CNS viral/mycoplasma infection
  - Has high sensitivity

Discussion

Meningitis

- Meningitis is an inflammation of the meninges in response to an infection.
- *Bacterial meningitis* is an acute purulent infection within the sub-arachnoid space.
- It is associated with a CNS inflammatory reaction that may result in *decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke.*
- The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction —*meningo-encephalitis*.
- The organisms most often responsible for community-acquired bacterial meningitis are
  - *Streptococcus pneumoniae (50%)*
  - *Neisseria meningitidis (25%)*
  - *Group B streptococci (15%), and*
  - *Listeria monocytogenes (10%).*
- **S. pneumoniae is the most common cause of meningitis in adults >20 years of age accounting for nearly half of the cases**

- *Haemophilus influenzae type b* accounts for <10% of cases of bacterial meningitis in most series.
- Also caused by viral infections (*HSV, Enteroviruses, HIV, VZV, etc*), fungal infections (*Cryptococcus neoformans in immune-suppressed host*) and M.TB.
- There had been multiple epidemic outbreaks of N.meningitidis and cause death to millions in Ethiopia.
- Ethiopia is one of the countries in the so called **"meningitis belt"** of the Sub-Saharan Africa. Several devastating epidemics have occurred cycling on an average of 8-12 years in this geographic area. One striking feature of the epidemic has been its seasonality by which it tends to occur during the dry and windy season between January and May. All regions of the country are at risk for meningitis outbreak.


Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Somalia
Ethiopia
Senegal
Gambia
Guinea-Bisseau
Guinea
Sierra Leone
Liberia
Côte d'Ivoire
Nigeria
Central African Republic
Cameroon
Burkina Faso
Benin
Togo
Ghana
Uganda
Kenya
Meningitis belt

Picture; Meningitis belt

- *Group B streptococcus, or S. agalactiae*, was previously responsible for meningitis predominantly in *neonates,* but it has been reported with increasing frequency in individuals *>50 years of age, particularly those with underlying diseases.*
- *L. monocytogenes is* an increasingly important cause of meningitis in *neonates (<1 month of age), pregnant women, individuals >60 years, and immuno compromised individuals of all ages.*
- *Staphylococcus aureus and coagulase-negative staphylococci* are important causes of meningitis that occurs following *invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intra-thecal chemotherapy.*

Meningitis Vs encephalitis

Meningitis	Encephalitis
Inflammation predominantly affecting the subarachnoid space	Inflammation of the brain parenchyma
Commonly caused by bacterial aetiologies	Caused by viral aetiologies
Nuchal rigidity is the prominent	➢ Presents with focal or generalized

symptom	neuropsychological dysfunction ➤ **Bizarre behaviour and confusion** are common features

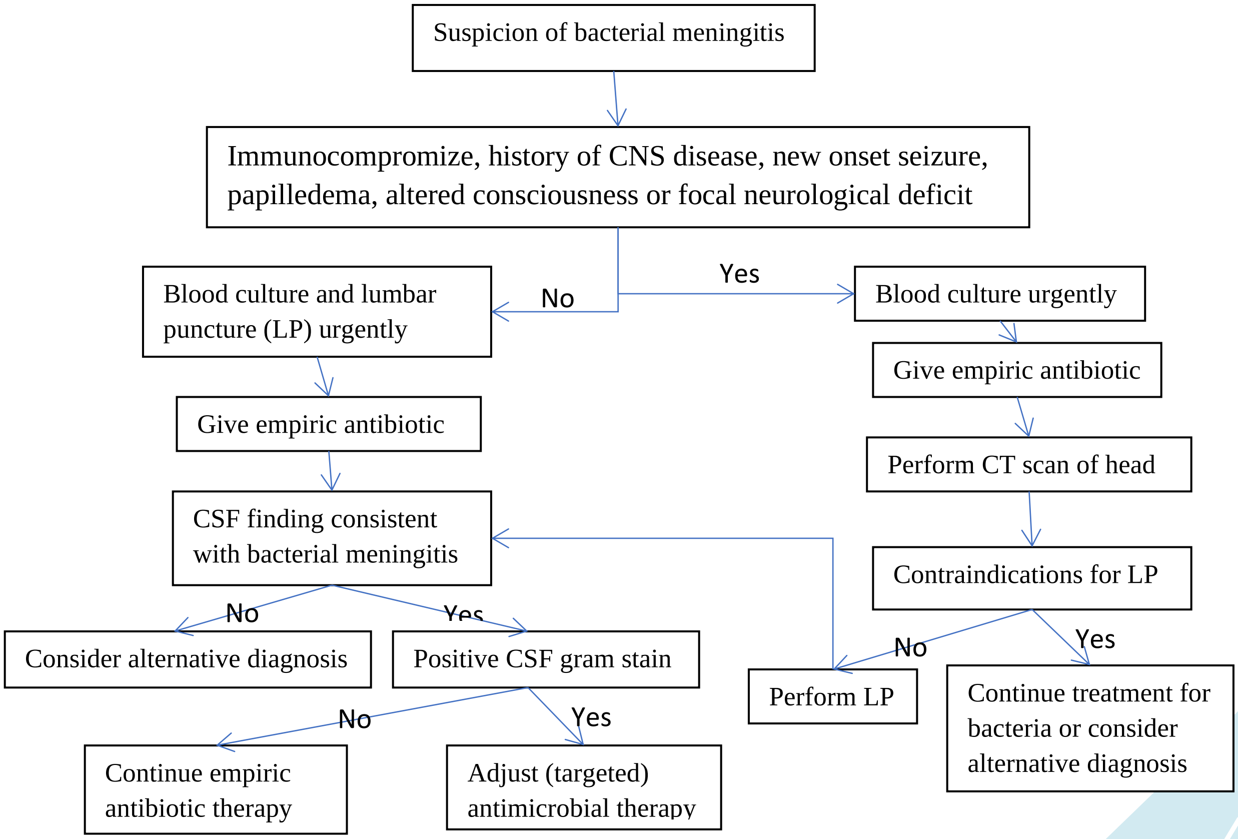
Pathophysiology

- Colonization of the nasopharynx by attaching to the epithelial cells
- Invasion of the intravascular space
- Avoid phagocytosis by neutrophils and complement mediated bactericidal activity in the bloodstream because of the presence of a polysaccharide capsule
- Directly infect choroid plexus epithelial cells to reach the CSF
- Multiply rapidly within the CSF due to the paucity of effective host immune defences in the CSF
- Bacterial proliferation induces inflammatory response and the formation of purulent exudate in the subarachnoid space

Clinical presentation and diagnosis → see the approach section above

Management of meningitis

Management algorithm for adults with suspected bacterial meningitis


Suspicion of bacterial meningitis
Immunocompromize, history of CNS disease, new onset seizure, papilledema, altered consciousness or focal neurological deficit
No
Yes
Blood culture and lumbar puncture (LP) urgently
Blood culture urgently
Give empiric antibiotic
Give empiric antibiotic
Perform CT scan of head
CSF finding consistent with bacterial meningitis
Contraindications for LP
No
Yes
Consider alternative diagnosis
Positive CSF gram stain
No
Yes
Perform LP
Continue treatment for bacteria or consider alternative diagnosis
No
Yes
Continue empiric antibiotic therapy
Adjust (targeted) antimicrobial therapy

Algorithm: Management algorithm for adults with suspected bacterial meningitis

- Acute bacterial meningitis is a medical emergency. In untreated cases the mortality approaches 100%.
- Institute empiric antimicrobial therapy promptly and adjust it after isolating the etiologic agent. Delayed treatment of bacterial meningitis results in an increased mortality (in-hospital mortality increases by 1.1 per hour of delay) and unfavorable outcomes at discharge.
- The duration of pathogen-directed therapy depends on the causative organism.

Supportive Therapy:

- Hydration: both under and over hydration may have unfavorable consequences. An IV maintenance fluid might be preferred over restricted fluid intake in the first 48 hours in settings with high mortality and lately presenting patients.
- Nutrition support if required (NGT if necessary)
- Analgesia and/or antipyretic:
  - Paracetamol, 1 g, PO, 4 - 6 hourly when required, with maximum daily dose of: 4 g in 24 hours.
  - Alternative: Ibuprofen, 400 mg, PO, TID with meals, if needed.
- Close supervision with regular monitoring of vital signs and neurological state.
- Institution of coma care for complicated cases.
- **The use of adjunctive corticosteroids is controversial**. Based on the existing current evidence they are not recommended in low- and middle-income countries as they do not demonstrated benefit
  - If used; Dexamethasone 10 mg IV QID for 04 days

Empiric antibiotic treatment

- The initial approach to treatment in a patient with suspected Acute bacterial meningitis includes performance of a LP to determine whether the CSF findings are consistent with the diagnosis (Algorithm above).
- **The duration of therapy is 10 to 14 days, for uncomplicated meningitis**. However, it can be adjusted depending on the specific causative pathogen, once identified (7 days for meningococcus and H. influenzae, 10-14 days for pneumococcus, up to 21 days for group B Streptococcus, Staphylococcus aureus, Listeria monocytogenes, and gram-negative meningitis.
- Immunosuppressed (HIV positive, uncontrolled diabetes, patients taking high dose corticosteroids) individuals may also need antifungal and/or viral coverage.

Table 1: Empiric antibiotic recommendations for acute bacterial meningitis*

Empiric therapy for COMMUNITY ACQUIRED acute bacterial meningitis

Population	Likely pathogen	First line	Second line

Age < 1 month (rarely up to 3 months)	Gram negatives Staphylococcus, Enterococcus, Pneumococcus	➢ Ampicillin, 150 to 200 mg/kg/day in divided doses every 3 to 4 hours, IV PLUS ➢ Cefotaxime, 225 to 300 mg/kg/day, IV, TID or QID Duration; for up to 21 days (if specific agent not identified)	➢ Ampicillin PLUS ➢ gentamycin, 2 to 2.5 mg/kg/dose, IV, TID OR ➢ Meropenem only ○ 40 mg/kg, IV, TID (maxi: 2g, TID)
1 month/3 months to 50 Years	S. pneumoniae, H. influenzae, Meningococcus	➢ Ceftriaxone, 100mg/kg/day, IV BID PLUS ➢ Vancomycin, 15 mg/kg/dose, IV, QID Duration; for 10-14 days (If specific agent not identified)	-
>50 years, alcoholism or other diseases of impaired imunity	S. pneumoniae, Meningococcus, Listeria, gram negative bacilli	➢ Ceftriaxone, 2 g, IV, BID Plus ➢ Ampicillin, 2g IV q4h PLUS ➢ Vancomycin, 1g, IV, BID Duration; for up to 21 days	➢ Ampicillin Plus ➢ Gentamycin, 5 mg/kg/day, IV, TID OR ➢ Ceftazidime, 2g IV, TID or QID With or without ➢ Vancomycin
Empiric therapy for HOSPITAL ACQUIRED acute bacterial meningitis (regardless of age)			
Hospital acquired meningitis/ ventriculitis, or for a patient with post- neurosurgery ventriculostomy/lumbar catheter, ventriculoperitoneal (atrial) shunt or penetrating trauma without basillar skul fracture. The likely pathogens are MDR gram negative pathogens like Acinetobacter, Pseudomonas, Klebsiella and MRSA		First Line	Second line
		➢ Vancomycin, 1g, IV, BID Plus ➢ Ceftazidime, 2g IV, TID or QID or ➢ Cefepime, 2 g IV, BID or TID Duration; for up to 21 days or individualized	➢ Vancomycin Plus ➢ Meropenem, 2g IV, TID Meropenem can be used in place of cefepime or ceftazidime if indicated by microbiologic data

***Penicillin allergy:**

- *Fluroquinolones for sever allergy (e.g anaphylaxis) in place of 3rd generation cephalosporins. Cephalosporin or carbapenems can be retained for mild cases (e.g. no hives or anaphylaxis etc).*
- *WHO recommends chloramphenicol as an alternative for penicillin allergy in meningitis endemic countries. However, recent data demonstrated increased mortality with CAF*
    - CAF, 500mg I.V. QID
- *For listeria, cotrimoxazole should be used in place of ampicillin.*
    - Cotrimoxazole, 20mg/kg/day, BID to QID

- **Vancomycin** should be added to either third generation cephalosporins or ampicillin if S.pneumoniae resistance in the locality is high, patient had prolonged or multiple antibiotics exposures within the past three months or for a patient with suspected coagulase negative staphylococcus infection or for any patient with high suspicion of MRSA
- **Acyclovir** 10mg/kg,IV (infuse over 1h) TID for 14-21d
  - This is added in a situation where HSV-1 encephalitis is likely. Early diagnosis and treatment are imperative. Mortality is reduced from >70% to <20% with IV acyclovir treatment.

Increased ICP

- Admit to ICU
- Elevation of the patient's head to 30-45^0
- Intubation and hyperventilation (Pa$_{co2}$ 25-30 mmHg)
- mannitol

Supportive Therapy

- Hydration: both under and over hydration may have unfavorable consequences.
- IV maintenance fluid IS preferred over restricted fluid intake in the first 48 hours in settings with high mortality and lately presenting patients.
- Nutrition support if required (NG tube feeding, if necessary)
- Analgesia and/or antipyretic:
  - Tepid sponging
  - Paracetamol oral, 1 g 4—6 hourly when required, maximum daily dose of: 4 g in 24 hours. Alternative: Ibuprofen, Diclofenac

Prevention

- Prophylaxis of contacts: Close household contacts for H. influenza and N. meningitides. eg. Ciprofloxacin, oral, 500 mg as a single dose.
- Avoiding sharing utensils or close contacts with people with upper respiratory tract infections.
- Prompt treatment of primary infection (e.g. upper respiratory tract infections)
- Using tissue or sleeve to cover sneezes and coughs and avoid kissing during infection.
- Avoiding overcrowding
- Proper hand washing and other peculiar precautions.
- Immunization as per national schedules (Ethiopia introduced H. influenza B vaccine (Hib) since 2007 and Pneumococcal Conjugate Vaccine (PCV) since 2013)
- Mass immunization if *N. Meningitis* epidemic (Men A vaccine is available in Ethiopia)

Special population considerations

Pregnant:

- Same principles as outlined in this topic can be used while aware of hemodynamics alterations during pregnancy.
- Floroquinolones and tetracyclines (if used required) are not recommended in pregnancy.
- Cotrimoxazole is not recommended in the third trimester of pregnancy to 6 weeks (age of infant) due to a risk of kernicterus in the infant.
- Caution should also be exercised in the use of aminoglycosides during pregnancy as they are rarely linked with hearing loss of infants.

Prognosis

- Mortality rate is
  - *3 - 7%* for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci
  - *15%* for that due to *L. monocytogenes*; and
  - *20%* for *S. pneumoniae*.
- Poor prognostic factors
  - *Decreased level of consciousness on admission*
  - *Onset of seizures within 24 h of admission*
  - *Signs of increased ICP*
  - *Young age (infancy) and age >50*
  - *The presence of co-morbid conditions including shock and/or the need for mechanical ventilation, and Delay in the initiation of treatment.*

Cryptococcal meningitis

Refer from chapter 5; RVI (click here → Cryptococcal meningitis)

TB Meningitis

Refer from Chapter 3; TB (click here → Tuberculous meningitis)

Chapter 9; CLD/ Chronic liver disease/ (የጉበት በሽታ)

Dr. Mulualem. G

Clinical features and how to write hx of CLD patient

History

- N.B. all the manifestations (history and P/E) we discussed here range from acute hepatitis to end stage cirrhosis. So, you have to correlate with your patient condition

- Pt's may present with
  - Abdominal distension
  - LOC in hepatic encephalopathy
- Abdominal distension
  - From which quadrant does the swelling starts? (left or right, upper or lower)
  - Gradual in onset
  - Painless
  - Persistent → increase in size and progress to involve the whole abdomen and lower extremities with in "X" months.
  - Together with dragging sensation and fullness in the left upper abdomen

What is the difference between abdominal swelling and abdominal distension?

- **Abdominal distension** occurs when gas (air) or fluid accumulates in the abdomen causing its outward expansion beyond the normal girth of the stomach. Underlying causes include ascites, Intestinal obstruction etc.
- The term **Abdominal swelling** is used when there is intraabdominal organ enlargement causing increased abdominal girth (e.g. hepatosplenomegaly) or mass arising from the abdomen
- Even though it's not correct, some authors use both terms interchangeably

- RUQ abdominal pain
  - Stabbing
  - Constant
  - Mild to moderate in severity
  - Radiates to the back
- Pruritis (itching sensation)
  - because of bile salt products deposited in the skin
  - Happen before jaundice

  - Cmn in cholestasis and it is the earliest smx of primary biliary cirrhosis
- Jaundice (yellowish discoloration)
  - Eye (sclera), skin
  - Progressively deepen
  - Ask who noticed the discoloration
- Dark (coca or tea colored) urine → due to bilirubinuria
- Stool colour change
  - Pale/tarry/clay coloured stool → due to urobilinogens or urobilins excretion in stool. **(for more click here** → Jaundice and hyper bilirubinemia)
  - Foul smelling
  - Scanty in amount
  - Melena or haematochezia
- Loss of libido, impotence, amenorrhea
- Hepatic encephalopathy features
  - Confusion
  - Sleep disturbance
  - Restlessness and aggressiveness
  - Difficult to concentrate
  - Forgetfulness
  - Abnormal body movement
  - LOC
    - While resting on bed or doing his/her daily activity
    - When does s/he gain consciousness?
    - Is there fall down injury or not?
- Other nonspecific smx's
  - Weight loss,
  - Nausea
  - Anorexia
  - Easy fatigability
  - Fever → high grade, intermittent, associated with chills, rigor and profuse sweating

N.B

- **Dark urine + jaundice is specific for liver disease**
- **smx's, signs and laboratory abnormalities should persist for ≥ 6months to consider CLD**

Clinical features based on type and duration of liver disease

Acute infection (Acute hepatitis)

- Largely asymptomatic
- Some patients may have: jaundice, nausea, vomiting, fatigue, RUQ abdominal pain.
- Rarely patients may progress to acute liver failure: encephalopathy, ascites, bleeding diathesis

Chronic infection (Chronic hepatitis)

- Largely asymptomatic
- Some patients may have non-specific symptoms which can be intermittent or persistent: fatigue/lack of energy, poor appetite

Decompensated Liver Cirrhosis

- Nonspecific symptoms: fatigue, weight loss, poor appetite
- Jaundice
- Ascites
- Variceal bleeding
- Encephalopathy (mild to severe)
- Bleeding

HCC (Hepatocellular Carcinoma)

- Weight loss
- Hard irregular liver mass on physical examination

Risk factors

- chronic alcohol intake and smoking
    - **Quantity and duration of alcohol intake** are the most important risk factors involved in the development of alcoholic liver disease.
    - gender is a strong determinant for alcoholic liver disease.
    - **Women are more susceptible to alcoholic liver injury** when compared to men. They develop advanced liver disease with substantially less alcohol intake
    - The recommendation is not to take alcohol. If not, A maximum 1 drink for women and 2 drinks for men per day.
        - One drink is roughly equivalent to a bottle of beer, a glass of wine, or a unit of spirit.
    - **significant alcohol intake (based on beer bottle)**
        - ✓ 1 bottle of beer contain 11-15 g of alcohol
        - ✓ women $\geq$ 2 bottle (22-30g) per day
        - ✓ men $\geq$ 3 bottle (33-45g) per day

Both of them should have taken these amount of alcohol for **≥ 10 years** to consider significant alcohol intake.

        - In men, 40 - 80 g/d of ethanol produces fatty liver; 160 g/d for 10 - 20 years causes hepatitis or cirrhosis (25-fold increased risk). Only 15% of alcoholics develop alcoholic liver disease.
        - Women exhibit increased susceptibility to alcoholic liver disease at amounts >20 g/d
        - Gender-dependent differences result from Poorly understood effects of estrogen and the metabolism of alcohol [by alcohol dehydrogenase].
    - In rough estimation One beer, 4 ounces of wine, or one ounce of 80% spirits all contain 12 g of alcohol.
    - How can we estimate the gram of alcohol from 1 bottle of Beer?
        - ✓ **If 1 bottle of beer = 330ml = have 5% alcohol**

          5% of 330ml = $\frac{5}{100}\, x\, 330ml = 16.5\, ml$

          1u = 1ml = 0.8 g

          16.5ml = ?

          16.5 x 0.8 g = 13.2 g

          So, 330ml of 5% alcohol beer contain approximately 13g alcohol
    - Approximate equivalent concentration of local alcoholic drinks with western drinks listed as follows
        - ✓ Tella with beer
        - ✓ Tejj (estimated 11 - 17 % alcohol) with wine
        - ✓ Areki (estimated 40 - 70 % alcohol) with spirits
    - The roles of beverage type(s), i.e. wine, beer, or spirits, and pattern of drinking (daily versus binge drinking) are less clear.
    - **CAGE criteria** to screen alcohol dependence/abuse
        - ✓ C → cutting down (assuming to decrease alcohol intake)
        - ✓ A → annoyance when criticized
        - ✓ G → guilty feeling
        - ✓ E → Eye openers (take alcohol in the morning motivation)
            - From these one +ve answer suggest alcohol use problem
            - ≥ 2 affirmative answer to CAGE suggest alcohol abuse or dependence
        - ✓ Also ask the following to asses alcohol dependence
            - Black outs (loss of memory during drinking)
            - Job loss
            - Marital conflict up to family loss
            - Legal problems
            - Drinking while driving or operating machinery
            - seizure
- obesity (high level of fat in the body)
- MSP, blood transfusion, tattoos, IV drug abuse, contact with jaundiced patient → risk of hepatitis virus infection
- Herbal medication use → herbal medicines are hepatotoxic

- Occupation → health care professionals
- Drugs
    - Carbamazepine → cholestatic jaundice
    - NSAID's (e.g. paracetamol) → hepatotoxic
    - Ant TB drugs especially pyrazinamide followed by INH are hepatotoxic
    - Methyldopa, ketoconazole → drug induced hepatitis
- Diet
    - Aflatoxin is RF for HCC
    - Iron → hemochromatosis
    - Previously Increased protein in diet was considered as a precipitant for HE. But currently understood that, *CLD patients are at risk of malnutrition, so don't restrict high protein diet)*
- Aetiologies
    - Family hx (genetics and inherited)
        - ✓ **Hemochromatosis**
        - ✓ **Wilson's disease**
        - ✓ **AAT (alfa 1 antitrypsin) deficiency**
        - ✓ NAFLD (non-alcoholic fatty liver disease) /NASH (Nonalcoholic steatohepatitis)
        - ✓ Primary biliary cirrhosis
        - ✓ PSC (primary sclerosing cholangitis)
        - ✓ Cystic fibrosis
    - Acquired
        - ✓ **Viral infections (HBV, HCV, CMV, EBV)**
        - ✓ **Alcoholic liver disease**
        - ✓ **Autoimmune hepatitis**

Liver cirrhosis and Complication of CLD

If the Clinical complications of cirrhosis become evident, the patient have Decompensated CLD

- Portal HTN related CXN
    - **Ascites,** Splenomegaly, hypersplenism
    - **SBP**
    - **Gastroesophageal varices**
    - **Hemorrhoids (rectal varices)**
    - Portal hypertensive gastropathy
- Hepatic insufficiency related CXN
    - **Hepatic encephalopathy (HE)**
    - Hepatopulmonary sxx (HPS)
    - Hepatorenal sxx (HRS) → Type I & Type II
    - Synthetic dysfunction
        - ✓ Hypoalbuminemia

- ✓ Coagulopathy → Factor deficiency, fibrinolysis, thrombocytopenia
- Malnutrition
- Hematologic abnormalities → Anemia, Hemolysis, Thrombocytopenia, Neutropenia
- Bone disease → Osteopenia, Osteoporosis, Osteomalacia

➢ **HCC (Hepatocellular carcinoma)**

✍ For more see the section below on Liver Cirrhosis and Complications of CLD with their Treatment

Sample history

Sample history of a patient from tach armachiho with the DX of Decompensated CLD (evidenced by ascites + Splenomegaly 2ry to portal HTN) secondary to Alcoholic Liver disease r/o Chronic viral hepatitis

Chief compliant

abdominal distension of 3 months duration

HPI

This patient was last relatively healthy 03 months back, at which time he noticed Abdominal distension which initially started from RLQ, which gradually increase in size and progress to involve the whole abdomen and lower extremities within one month duration. Together with dragging sensation in the left upper abdomen, sense of fullness and early satiety.

Four months before the onset of abdominal distension, he experienced a stabbing RUQ abdominal pain which is moderate in severity and radiates to the back associated with low grade intermittent fever, coca colored urine and his families accidentally noticed yellowish discoloration of his eyes but no stool color change or itching sensation. He has also unquantified but significant weight loss to the extent his trousers become loose, loss of appetite and easy fatigability.

For these, he visited a traditional healer where he was given unspecified herbal medication and cauterized at his arms, forearms, over the abdomen and back but he didn't get any relief. Finally, he came to our hospital for better investigation and management.

- He drinks traditional areki half bottle 2 - 3 times per week for 5 years and then changed his drink to a beer of 10 to 15 bottles every Tuesday, Saturday and Sunday (average 37 bottles per week) for the past 8 years that means he drinks for a total of 13 years. which is estimated to be 70g alcohol intake daily for 13 years. *(RF, hint for estimation; 37* *bottles divided by 7 days = 5.3 bottles daily, estimated alcohol content of one bottle is 13.2 g → look at RF section above, 5.3 x 13.2 g = 69.77 g ≈ 70g)*

- No hx of blood transfusion, tattooing, contact with a jaundiced patient, IV drug abuse or MSP, *(RF for hepatitis virus transmission)*
- No hx of drug intake other than mentioned above *(mentioned above under RF of CLD)*
- No family hx of similar illness *(genetics → etiology)*
- He usually eats injera made of "teff" and "machilla" and "wott" made of "atter" and "dagusa" 3-4 times per day. Occasionally he eats meat during holidays *(aflatoxin is RF for HCC, hemochromatosis)*
- No hx of reddish discoloration of urine, pain during urination, urgency, frequency or flank pain *(HRS → CXN)*
- No hx of nasal bleeding, bloody vomiting or melena *(bleeding tendency from coagulopathy, variceal bleeding/painless, coffee ground appearance,nonprojectile/ → CXN)*
- No hx of tinnitus, blurring of vision, light headedness or easy fatigability *(anaemia 2ry to blood loss especially in variceal bleeding which may lead to shock, vitamin B12 deficiency or IDA → CXN)*
- No hx of sleep disturbance, confusion, Forgetfulness, Abnormal body movement or LOC *(HE → CXN)*
- Has hx of river water contact but no hx of post river water contact itching *(HSS → DDX)*
- No hx of dyspnea, orthopnea, PND or palpitation *(CHF → DDX)*
- No hx of chronic cough, contact with chronic cougher or previous TB treatment
- No self/family hx of DM, HTN or asthma *(DM cause Fatty liver disease, NAFLD in HTN and metabolic sxx)*
- He was screened for RVI 2 months back and found to be NR.

Finally, He was admitted to our hospital supported physically by his families

Physical examination (pertinent findings)

1 GA

- Chronically sick looking
- Fetor hepaticus → Musty odor in breath as a result of increased dimethyl sulfide.

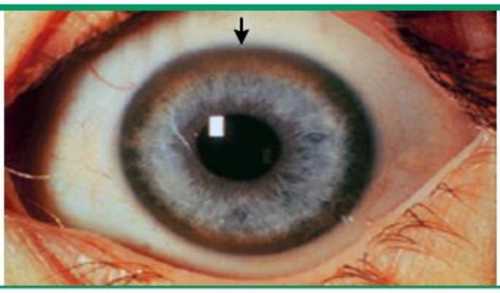
2 Vital signs

- Tachypnea (kusmauls breathing) → HE
- Febrile → hepatitis
- Orthodeoxia
- BMI may be misinterpreted due to edema. But, if BMI is very low even in ascites, it indicates significant weight loss

3 HEENT

- Icteric sclera (jaundice)
- Pale conjunctiva (anaemia) 2ry to
  - ✓ Variceal bleeding
  - ✓ Hypersplenism
    - Splenomegaly + pancytopenia + normal cellular BM (compensatory proliferative response in BM)
    - Cell count corrected in post splenectomy
  - ✓ Nutritional deficiency → IDA, Vitamin B12 deficiency
  - ✓ Direct alcohol toxicity to BM
- Epistaxis
- Xanthelasma in eye and hand crease
- Kayser fleischer ring on cornea during slit lamp examination → Wilson's disease

Kayser-Fleischer ring



Kayser-Fleischer ring (arrow) in a patient with advanced neuropsychiatric Wilson disease. The dense brown copper deposits encircle the iris. It is rare to see Kayser-Fleischer rings without the aid of a slit lamp examination because Wilson disease is usually recognized at an earlier stage when the rings are not as prominent.

LGS

- Gynecomastia in males
  - This is caused by increased estradiol due to decreased estrogen metabolism in liver
  - can occur in up to 66% of patients.
  - Rarely from side effect of spironolactone treatment for ascites
- Parotid enlargement
  - likely due to alcohol use and not cirrhosis per se.
  - ?2ry to collagen deposition
- Testicular atrophy → due to hyper estroginism (estradiol)

5 RS

- kusmauls breathing → acidosis 2ry to HE
- cyanosis
- clubbing
- pleural effusion → right sided and transudative effusion due to local extension from ascites through diaphragmatic pores

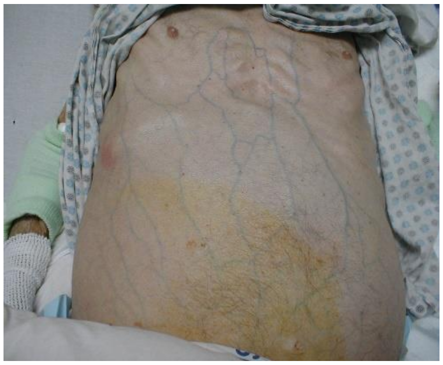
6 CVS

- cording of arteries because of fat malabsorption → fat streak

- RSHF as a cause of cardiac cirrhosis or LSHF result in → pulmonary HTN → RSHF → cardiac cirrhosis

7 Abdominal examination

- HSM (hepatosplenomegaly) → liver size Can be enlarged, normal, or shrunken
  - later liver may not be palpable due to end stage cirrhosis
  - splenomegaly is 2ry to portal HTN
- Ascites
  - symmetrically distended abdomen
  - flanks are full
  - eversion of umbilicus with transverse or circular slit
  - fluid thrill and shifting dullness
  - superficially distended and tortuous abdominal vessels
    - ✓ drain away from umbilicus during palpation which indicate portal HTN (William Harvey method)



  - straie alba/atrophica

    N.B
    - ✓ *Straie gravidarum→ in pregnancy*
    - ✓ *Purple straie → cushing sxx*
- caput medusae
  - Latin word for head of medusa. **In cirrhosis, distended and engorged superficial epigastric veins which are seen radiating from umbilicus across the abdomen and apparently similar to medusa head**
  - In portal hypertension, the umbilical vein may open.
  - Blood from the portal venous system may be shunted through the periumbilical veins into the umbilical vein and ultimately to the abdominal wall veins, manifesting as caput medusa.

Picture; caput medusae (head of medusa) from Greek mythology, which had venomous snakes in place of hair

- bruit over the liver 2ry to HCC
- tenderness and rebound tenderness → SBP
- hemorrhoid in DRE

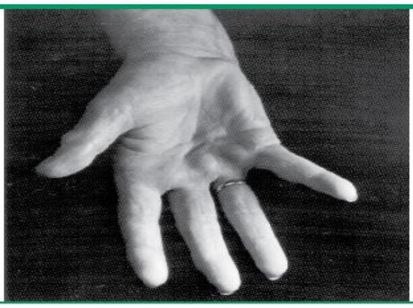
8 GUS

- Loss of male type hair distribution (i.e. pubic hair loss)
- Testicular atrophy → due to hyper estroginism (estradiol)
- Amenorrhea or menorrhagia in females

9 MSS

- Bilateral pitting leg oedema
- Dupytren's contracture
    - Thickening and shortening of palmar fascia that leads to flexion deformities of the fingers.
    - Thought to be caused by fibroblastic proliferation and disorderly collagen deposition.
    - It is relatively common (33% of patients).
    - Cmn in alcoholics

Dupuytren's contracture



Nodular fibrosing lesions with bands radiating distally are features of Dupuytren's contracture. The ulnar side of the hand is affected, with the fourth and fifth fingers usually involved first.

- Thenar and hypothenar muscle atrophy

10 IS

- Spider angioma or spider nevi
    - Telangiectasia which consist of central arteriole with radiating small vessels because of an increase in estradiol.
    - Occur in about 1/3 of cases
    - Found in the distribution of SVC (i.e. above the nipple line)
    - May be found in Rheumatoid arthritis, thyrotoxicosis, pregnancy

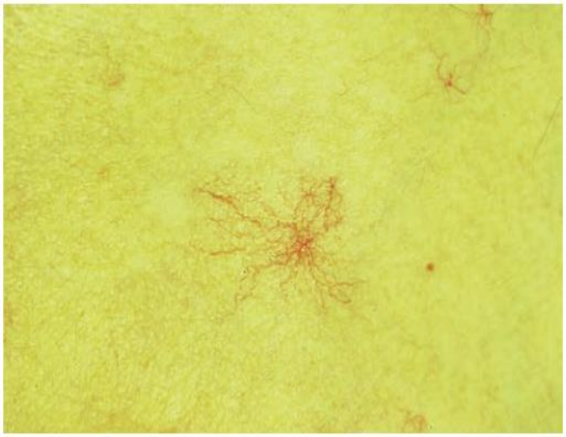
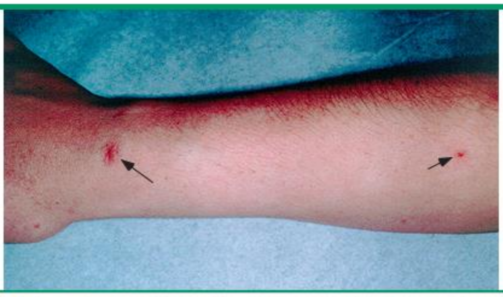


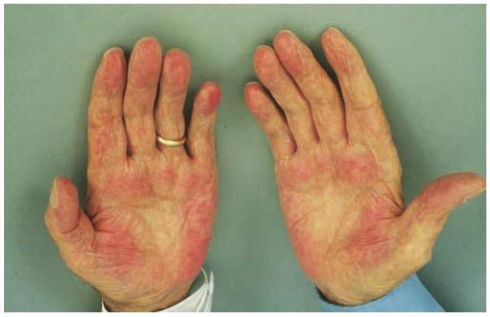
FIGURE 337-2 Spider angioma. This figure shows a spider angioma in a patient with hepatitis C cirrhosis. With release of central compression, the arteriole fills from the center and spreads out peripherally.

Spider angiomas



This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left. Pressure over the central vessel with the end of a paper clip or a glass slide causes the entire lesion to blanch. Similar lesions can be seen in patients with cirrhosis, and are most commonly seen on the upper chest, face, and back.

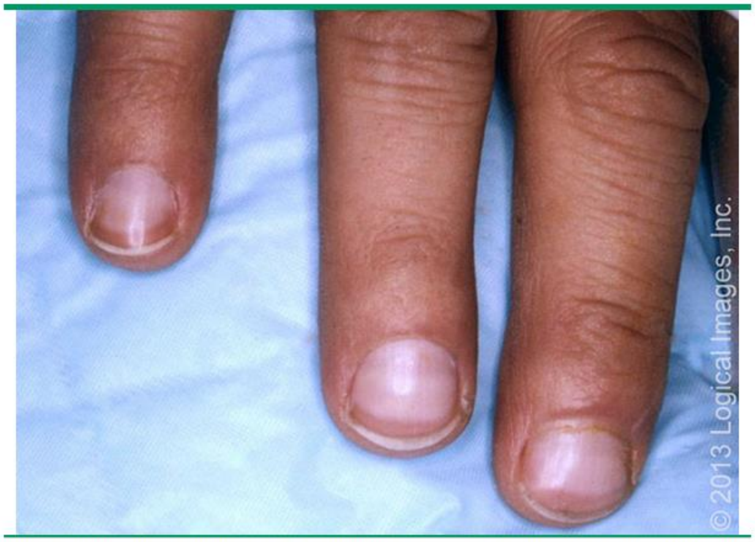
- Palmar erythema → Exaggerations of normal speckled mottling of the palm, because of altered sex hormone metabolism.



Figure; **Palmar erythema**. This figure shows palmar erythema in a patient with alcoholic cirrhosis. The erythema is peripheral over the palm with central pallor.

- Leukonychia (from Greek word leuko → white, nychia → nail) and terry nails

Terry nails



Patients with cirrhosis may have a finding known as Terry nails. In patients with Terry nails, the proximal two-thirds of the nail plate appears white, whereas the distal one-third is red. This finding is believed to be secondary to a low serum albumin. Terry nails may also be seen in patients with renal failure, diabetes, and heart failure.

- Palmar pallor
- Skin pigmentation → in hemochromatosis
- Bruising / purpura
- Axillary and pubic hair loss
- Scratch marks due to pruritis

11 NS → usually HE features

- Asterixis
  - Bilateral asynchronous flapping of outstretched, dorsiflexed hands seen in patients with HE.
  - Asterixis can be elicited by having patients **extend their arms and bend their wrists back.**
  - In this maneuver, patients who are encephalopathic have a **"liver flap" – i.e., a sudden forward movement of the wrist.**
  - *This requires patients to be able to cooperate with the examiner and obviously cannot be elicited in patients who are severely encephalopathic or in hepatic coma.*
- Construction apraxia
- Coma
- hyperreflexia

N.B

- physical examination findings related to hyper estroginism in males (especially in alcohol users) include
  - Gynecomastia
  - Testicular atrophy
  - Loss of male pattern hair distribution
- Peripheral **Stigmata of liver disease**
  - HANDS:
    - ✓ Palmar Erythema
    - ✓ Clubbing
    - ✓ Dupytrens
    - ✓ Leuconychia
    - ✓ Flapping tremor
  - HEENT/UPPER BODY
    - ✓ Jaundice
    - ✓ Spider Angiomata
    - ✓ Gynaecomastia and scant body hair
    - ✓ Scratch marks
  - ABDOMEN
    - ✓ Ascites
    - ✓ Hepatosplenomegally
    - ✓ Caput Medusa
    - ✓ Hemorrhoids on PR
    - ✓ Small testes

DDX

DDX for patients presenting with abdominal distension (ascites)

- CLD 2ry to
  - **Viral hepatitis**
  - **Alcoholic liver disease**
  - **Autoimmune hepatitis**
  - **HSS**
    - ✓ hepatocellular function remains normal and cirrhosis is rare
    - ✓ Chronic schistosomiasis after 5-10 years
    - ✓ **Post river water contact itching may be forgotten so, endemicity is important than asking post river water contact itching (e.g. living around lake tana)**
    - ✓ Phases of schistosomiasis
      - Dermatitis/swimmer's itch
        - popular pruritic rash at skin penetration site in 24-48hrs
      - Katayama fever
        - serum sickness like illness
        - associated with excess antigenemia and formation of soluble immune complexes
      - Chronic schistosomiasis
    - ✓ Granulomatous reaction around the ova results **in organomegaly, obstruction and fibrosis**
    - ✓ Fibrosis of the portal veins known as **periportal fibrosis or Symmers' clay pipe—stem** which result in **portal HTN** (which in turn result in **ascites, varices & splenomegaly)**
    - ✓ Similar pathologic changes occur in other organs also
      - **bladder → obstructive uropathy, urosepsis, risk of bladder cancer (SCC). S.hematobium is the etiologic agent**
      - Lung → pulmonary HTN and corpulmonale
      - Brain and spinal cord → transverse myelitis
      - GIT — **bloody diarrhea** and abdominal pain
      - For more click here and refer '' Intestinal Helminthic Infestations (የአንጀት ጥገኛ ተውሳክ ፣የአንጀት ትላትል) *and blood flukes* section from Short case of Nitsibin → Schistosomiasis (ቢሊሃርዚያ)
  - **Drug associated chronic hepatitis**
    - Direct toxic effect (Dose dependent) → Acetaminophen, Carbon tetrachloride
    - Idiosyncratic → isoniazid, valproate, phenytoin, Ciprofloxacin, Augmentin

  - Other → Estrogenic/androgenic steroids, pyrazinamide, methotrexate
- **HCC** → usually a complication of cirrhosis
- **Genetics**
  - ✓ **Hereditary Hemochromatosis**
  - ✓ **Wilson disease**
  - ✓ **AAT (α_1 antitrypsin) deficiency**
  - ✓ cystic fibrosis
- Cardiac cirrhosis
- Metabolic disorders
  - NAFLD (non-alcoholic fatty liver disease)
  - NASH (non-alcoholic steatohepatitis)
- Infiltrative disorders
  - Lipid storage diseases (Gaucher's and Niemann-Pick disease)
  - Amyloidosis
  - sarcoidosis
- Budd chiarri SXX
  - ✓ Hepatic vein outflow obstruction by thrombus
  - ✓ Triads include
    1. Abdominal pain
    2. Ascites
    3. hepatomegaly
  - ✓ Other manifestations
    - Jaundice
    - Splenomegaly
    - encephalopathy
- Cryptogenic chronic hepatitis
- Idiopathic

- TB peritonitis
  - ✓ disseminated TB to liver and peritoneum
  - ✓ present with **very huge ascites**
  - ✓ cmn in our setup
- lymphoma
  - ✓ peritoneal carcinomatosis causing ascites with liver involvement
- RSHF
- Constrictive pericarditis
- Nephrotic sxx
- Chronic pancreatitis
- Meig's sxx → ovarian ca + pleural and peritoneal effusion
- IVC sxx
- Hypothyroidism → rare
- PLE (protein losing enteropathy) → very rare condition

N.B

6F'S in abdominal distension

- Fluid → ascites
- Feces → failure to pass feces but no flatus indicates incomplete intestinal obstruction
- Flatus → failure to pass both feces and flatus indicates complete intestinal obstruction
- Fat → obesity
- Fetus → pregnancy
- Fatal growth → organomegaly, malignancy, AAA (abdominal aorta anourysm)

DDX for HE presenting with LOC

- HE
- Cerebral malaria
- Acute alcohol toxicity
- SDH
- Meningoencephalitis
- DKA
- Metabolic encephalopathy
- Sedation overdose

DDX for oesophageal varices presenting with upper GI bleeding

- Oesophageal varices
- PUD
- Mallory Weiss tear
- Erosive esophagitis
- Gastric ca
- Gastro duodenal erosions

For more refer under short case of nitsibin (click here → Upper GI bleeding)

N.B

Portosystemic anastomotic area include

- Haemorrhoidal plexus
- Gastro oesophageal junction
- Retroperitoneal area
- Peri umbilical area

DDX for hepatomegaly with cirrhosis

- Alcoholic liver disease
- Infiltrative conditions
    - Hemochromatosis
    - Wilson disease
    - sarcoidosis
- HCC coming after cirrhosis
- Cirrhosis in early stage

Ass't example

Decompensated CLD (evidenced by ascites + SBP + Splenomegaly 2ry to portal HTN) secondary to Alcoholic Liver disease r/o Chronic viral hepatitis

IX

1. **LFT and liver enzymes** → *for normal values refer short case of nitsibin (click here* → Chapter 11; Reference Intervals for Laboratory Tests*)*
    - LFT
        - **Serum bilirubin level → indicates metabolic activity**
        - **Albumin and total protein → indicates synthetic function**
        - **PT, aPTT and INR** → prolongs earlier than hypoalbuminemia, also **indicates synthetic function**

N.B

☛ albumin completely synthesized by liver. But globulin synthesized also by lymphoid tissue. So, in CLD there will be low albumin/due to impaired synthetic function of the liver / with high globulin.

- ☛ **Unconjugated (indirect) hyperbilirubinemia is present when the direct fraction is <15% of the total serum bilirubin.**

$$i.e\ \ ratio = \frac{direct\ bilirubin}{Total\ bilirubin}\ x\ 100\ \%$$

$$Ratio\ > 15\%\ implies\ direct\ hyperbiliribinemia$$

$$Ratio\ < \ 15\%\ implies\ indirect\ hyperbiliribinemia$$

- Liver enzymes → determines the extent of liver damage
  - ✓ **ALT (SGPT)** → specific to liver
    - ○ Elevates in hepatocellular disorders than extra hepatic or Intrahepatic obstructive disorders
    - ○ Stays longer and higher than AST
  - ✓ **AST (SGOT)**
    - ▪ nonspecific which may occur in myolysis
    - ▪ Viral hepatitis - may reach 10 to 100 times ULN (Upper normal limit)
    - ▪ Cirrhosis - 4 times ULN
    - ▪ AST: ALT ratio = 2:1 (ratio >1) is typical for alcoholic liver disease, for others ALT > AST
    - ▪ In alcoholic hepatitis and in contrast to other causes of fatty liver, *The AST and ALT are usually elevated 2 to 7-fold* (rarely >400 IU).
  - ✓ ALP
    - ▪ **Significantly elevated** than other enzymes **in obstructive jaundice**
      - ○ Predominant in obstructive conditions than in hepatocellular disorders - 3 to 10 times ULN
      - ○ Hepatocellular disorders - <3 times ULN.
    - ▪ Also found in intestine, bone and placenta
    - ▪ Simultaneous measurement with GGT confirm liver disease
  - ✓ GGT/GGTP
    - ○ Correlates with ALP levels
    - ○ **Elevated in biliary obstruction (Obstructive jaundice)**
    - ○ **Typically, much higher in CLD from alcohol**

N.B

In Hepatocellular pattern of jaundice ALT/AST elevated out of proportion to ALP and the reverse is true in cholestatic pattern of jaundice.

(AST → aspartate aminotransferase = SGOT → serum glutamate oxaloacetate transaminase, ALT → alanine aminotransferase = SGPT → serum glutamate pyruvate transaminase, *ALP → alkaline phosphatase, GGT/GGTP → Gamma-glutamyl transferase / γ-glutamyl transpeptidase)*

2. **Viral markers**
    - **HB_sAg**
        - ✓ First evidence of infection (before biochemical abnormality)
        - ✓ Signifies Infection & implies infectivity
        - ✓ Commonly done in our setup
    - HB_cAg → Induces cellular immune response
    - HB_eAg → Marker for active viral replication / INFECTIVITY
    - HB_xAg
    - Anti **HB_sAg**
        - ✓ Antibody which confers PROTECTIVITY
        - ✓ signifies recovery from HBV infection, non-infectivity, vaccination
    - Anti HB_cAg
        - ✓ Antibody detected in anyone with previous exposure
        - ✓ Does NOT confer protectivity
        - ✓ IgM → acute infection / lasts 3-6 months.
        - ✓ IgG → implies chronic hepatitis infection
        - ✓ present in "window period"
    - Anti HB_eAg
        - ✓ Antibody which indicates antigen is cleared / virus not replicating
        - ✓ Decrease infectivity
    - HBV DNA (PCR) → Best indicator of viral replication, Usually parallel's HB_eAg
    - HCV RNA (PCR)
3. **Ascitic fluid analysis** → refer short case of nitsibin (click here → Ascitic fluid analysis*)*
4. **CBC**
    - Anaemia 2ry to
        - ✓ Variceal bleeding
        - ✓ Hypersplenism
            - ▪ Splenomegaly + pancytopenia + normal cellular BM (compensatory proliferative response in BM)
            - ▪ Cell count corrected in post splenectomy
        - ✓ Nutritional deficiency → IDA, Vitamin B12 deficiency
        - ✓ Direct alcohol toxicity to BM
    - Leukocytosis in SBP
    - Thrombocytopenia or pancytopenia
    - Macrocytosis in the absence of anaemia → alcoholic liver disease or from Vitamin B12 deficiency
5. **PM (peripheral morphology)**
    - Microcystic hypochromic anaemia → IDA
    - Macrocytosis /megaloblastic anaemia/ → Vitamin B12 deficiency
6. **Co-infection: HIV and HCV screening**
7. **Serum electrolyte**
    - Hypokalaemia which cause HE by

        i. Resulting systemic alkalosis which prevent conversion of NH_3 (toxic ammonia) to NH_4 (non-toxic ammonia)
        ii. Directly stimulate renal ammonia production
    - Hyponatremia → from diuretic effect, liver disease by itself (due to inability to excrete free water resulting from high levels of ADH and aldosterone)

8. **U/A** → Bilirubinuria /can be detected in dipstick examination/, toxins, copper and ceruloplasmin
9. **Abdominal U/s**
    - Show **architecture of liver** i.e. **cirrhotic change in liver** (*where it may show a small and nodular liver in advanced cirrhosis along with increased echogenicity with irregular appearing areas*),
    - **Determine size of portal vein or portal vein dilatation and HVPG for Portal HTN diagnosis.**
        - A normal Hepatic venous pressure gradient (HVPG) is between 1 and 5 mmHg.
        - Portal hypertension is present if the HVPG is ≥6 mmHg. Portal hypertension typically becomes clinically significant when the HVPG is ≥10 mmHg
        - On the other hand, portal HTN can be diagnosed if portal vein diameter is > 12mm, it strongly suggests portal HTN if diameter is > 15mm.
    - To detect intra-abdominal mass (**HCC**, lymphoma) and LAP
    - **Detecting fatty infiltration of the liver in NAFLD/NASH.**
    - Screen for Budd-Chiari syndrome (by assessing flow in the hepatic vein)
    - Can detect minimal ascites as little as 100ml of ascitic fluid (ascites can be appreciated by physical examination /to detect flank dullness/ if the fluid volume is ≥ 1500ml)
10. **CXR, ECG, ECHO** → if RSHF suspected only
11. **Serum ferritin level, Transferrin saturation** → if hereditary hemochromatosis suspected. Both of these will be elevated in symptomatic patient
    - Transferrin saturation = $\frac{\textbf{Serum Iron}}{\textbf{TIBC(Total iron binding capacity)}} X\ 100\ \%$
    - ferritin is an acute-phase reactant and can be elevated in RA, lymphoma or other cancers, in NASH (Nonalcoholic steato hepatitis) patient in the absence of iron overload
    - If the ferritin is >1000 g/L, considered liver biopsy to look for iron deposition
12. **serum AAT and serum albumin level**
13. **Serum ceruloplasmin and copper level**
    - Ceruloplasmin is transport protein of copper
    - Decreased ceruloplasmin and increased serum copper level expected in Wilson disease
14. **Serum autoantibodies (like ANA)** → if autoimmune hepatitis is suspected
15. **Abdominal CT and MRI** → Screening for HCC if clinical suspected: If there is liver mass (CT scan of the abdomen with or without alpha fetoprotein)
16. **Upper GI endoscopy and proctoscopy**

- For oesophageal varices and haemorrhoid respectively
- Usually used for mgt purpose rather than Ix especially upper GI endoscopy for endoscopy guided ligation of variceal bleeding

17. **EEG** → for HE grading, usually not done in our setup
18. **Serum alfa feto protein (AFP) level** → for HCC
19. **Liver biopsy**

- Important for alcoholic liver disease
- **The gold standard for diagnosis of cirrhosis is a liver biopsy**, through a percutaneous, trans jugular, laparoscopic, or fine-needle approach. **But biopsy is not necessary if the clinical, laboratory, and radiologic data suggests cirrhosis.**
- Furthermore, there is a small but significant risk to liver biopsy, and cirrhosis itself predisposes for complications due to liver biopsy.
- **Depending on the size of the nodules there are three macroscopic types of cirrhosis:**
  - **Micronodular cirrhosis** (Laennec's cirrhosis or portal cirrhosis): regenerating nodules are **< 3 mm.**
  - **Macronodular cirrhosis** (post-necrotic cirrhosis): The nodules are **> 3 mm**
  - **Mixed cirrhosis: Consists in a variety of nodules with different sizes.**

N.B

Non-invasive screening for liver fibrosis: use one of the score available e.g. APRI score

- **APRI Score**

$$\boldsymbol{APRI\ score} = \frac{\left[\dfrac{\mathbf{AST}}{\mathbf{UNL\ of\ ALT}}\right] \boldsymbol{x}\ \mathbf{100}}{\mathbf{platelet\ count\ (109/L)}}$$

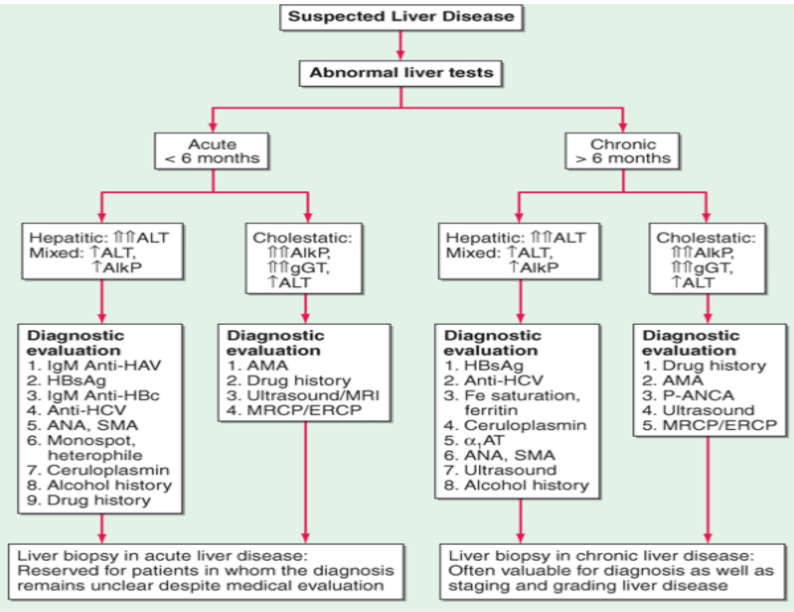
  - APRI >0.5 but ≤ 1.5: Significant fibrosis or cirrhosis possible
  - APRI >1.5 but ≤ 2: Likely significant fibrosis, cirrhosis possible
  - APRI >2: Likely cirrhosis

  Upper Normal limits (UNL) for normal ALT

  - 30 U/L for men and 19 U/L for women
  - Use the above cut point rather than the highly variable upper normal limits of different laboratories.

- **Transient elastography (Fibro scan)** if readily available

Evaluation of abnormal liver tests


Suspected Liver Disease
Abnormal liver tests
Acute < 6 months
Chronic > 6 months
Hepatitic: ⇑⇑ALT Mixed: ↑ALT, ↑AlkP
Cholestatic: ⇑⇑AlkP, ⇑⇑gGT, ↑ALT
Hepatitic: ⇑⇑ALT Mixed: ↑ALT, ↑AlkP
Cholestatic: ⇑⇑AlkP, ⇑⇑gGT, ↑ALT
Diagnostic evaluation 1. IgM Anti-HAV 2. HBsAg 3. IgM Anti-HBc 4. Anti-HCV 5. ANA, SMA 6. Monospot, heterophile 7. Ceruloplasmin 8. Alcohol history 9. Drug history
Diagnostic evaluation 1. AMA 2. Drug history 3. Ultrasound/MRI 4. MRCP/ERCP
Diagnostic evaluation 1. HBsAg 2. Anti-HCV 3. Fe saturation, ferritin 4. Ceruloplasmin 5. α1AT 6. ANA, SMA 7. Ultrasound 8. Alcohol history
Diagnostic evaluation 1. Drug history 2. AMA 3. P-ANCA 4. Ultrasound 5. MRCP/ERCP
Liver biopsy in acute liver disease: Reserved for patients in whom the diagnosis remains unclear despite medical evaluation
Liver biopsy in chronic liver disease: Often valuable for diagnosis as well as staging and grading liver disease

Discussion

Chronic liver disease (CLD)

- CLD encompasses a wide spectrum of disorders including infectious, metabolic, genetic, drug-induced, idiopathic, structural and autoimmune diseases.
- It includes
  - Chronic Hepatitis
  - Cirrhosis
  - Hepatocellular Carcinoma

9.1 Liver Cirrhosis and Complications of CLD with their Treatment

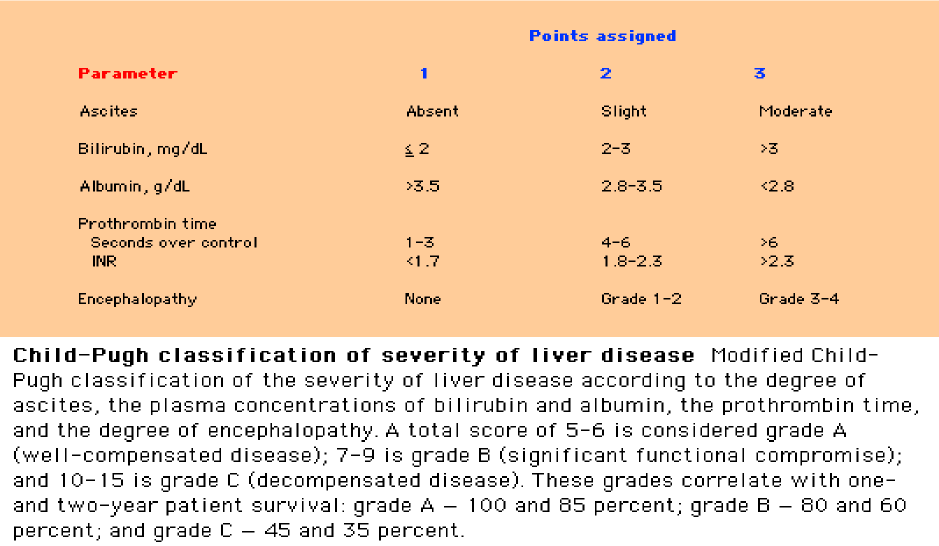
Cirrhosis

- **Definition:** irreversible, chronic parenchymal injury with fibrosis and nodular degeneration causing distortion of vascular bed of liver & disorganization of normal architecture.
- Cirrhosis represents a late stage of progressive hepatic fibrosis with distortion of the architecture of the liver with formation of regenerative nodules.

- It can result from any cause of chronic liver disease e.g. chronic viral hepatitis, alcoholic liver disease.
- Patients with cirrhosis develop a variety of complications which cause marked morbidity and mortality.
    - The common complications include ascites, SBP, variceal bleeding, HE, HRS and HCC.
- Causes of cirrhosis
    - Alcoholism
    - chronic viral hepatitis (Hep. B &C)
    - Autoimmune hepatitis
    - nonalcoholic steatohepatitis
    - biliary cirrhosis
        - Primary biliary cirrhosis
        - Primary sclerosing cholangitis
    - cardiac cirrhosis
    - Inherited metabolic liver disease
        - Hemochromatosis
        - Wilson's disease
        - AAT deficiency
        - Cystic fibrosis
- Factors which lead to cirrhosis include
    - Viral factors → HBV
    - Host factors
        - Immunosuppression
        - NAFLD
        - Chronic alcohol intake
        - Hepatotoxic drugs
        - Concomitant infection → HBV + HCV, HBV+HDV
    - External factors

Childs-Pugh classification

- Don't try to rehearse this, just know the name and the principle only.
- It is a scoring system used to assess how risky surgery will be in pts with liver disease
- MELD scores and MAYO scores used to assess pts for liver transplant and transplant allocation



	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds over control	1-3	4-6	>6
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh classification of severity of liver disease Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent.

General management principle for CLD and cirrhosis

- Generally, liver damage from cirrhosis cannot be reversed, but treatment could stop or delay further progression and reduce complications.
- **A healthy diet** is encouraged, as cirrhosis may be an energy-consuming process.
    - Weigh the risk and benefit of low protein diet (i.e. fear of encephalopathy in high protein diet, but malnutrition risk of CLD by itself requiring high protein diet).
- Bed rest or hospitalization
    - for poor oral intake (need for IV medication), significant vomiting.
    - Patients with decompensated cirrhosis generally require admission to hospital, with close monitoring of the fluid balance, mental status, and emphasis on adequate nutrition and medical treatment.
- Maintain ABC of life in patient presenting with severe and life-threatening complications
- Monitor weight and vital sign regularly
- IV dextrose for patients with poor oral intake.
- **Avoid administration of saline** as it would add to the already high total body sodium content that typically occurs in cirrhosis.
- Avoid constipation and other precipitants of HE. Laxatives, such as lactulose, decrease risk of constipation.
- Avoid alcohol, smoking and other identified risk factors
- Identifying and treatment of Specific underlying cause of CLD
- Preventing further liver damage
    - Regardless of underlying cause of cirrhosis, alcohol and paracetamol, as well as other potentially damaging substances, are discouraged.
    - Vaccination of susceptible patients should be considered for Hepatitis A and Hepatitis B.
- Identifying and treatment of cxn

- Close follow-up

9.1.1 Portal hypertension related cxn

9.1.1.1 Portal Hypertension

- Portal hypertension is defined as the elevation of the **hepatic venous pressure gradient (HVPG) to >5 mmHg.**
    - HVPG is defined as the difference in pressure between portal vein and inferior vena cava.
    - HVPG is used as a measure of portal venous pressure. **A normal HVPG is between 1 and 5 mmHg.**
- **Portal hypertension is present if the HVPG is ≥6 mmHg. Portal hypertension typically becomes clinically significant when the HVPG is ≥10 mmHg, at which point varices may develop. Once the HVPG is ≥12 mmHg, patients are at risk for variceal bleeding and the development of ascites.**
- There are two simultaneously occurring processes in the pathogenesis of Portal hypertension. These are;
    - Increased intrahepatic resistance to the passage of blood flow through the liver
    - Increased splanchnic blood flow secondary to vasodilation
- In industrialized countries, portal hypertension is typically the result of cirrhosis, with noncirrhotic portal hypertension accounting for < 10 % of cases. In other parts of the world, noncirrhotic portal hypertension due to causes such as schistosomiasis and portal vein thrombosis are the leading causes of portal hypertension
- The causes of portal hypertension can be:
    - Prehepatic
    - Intrahepatic
    - Post hepatic

Table; Classification of Portal Hypertension	
	Causes
I. Prehepatic	➢ Portal vein thrombosis ➢ Splenic vein thrombosis ➢ Massive splenomegaly (Banti's syndrome)
II. Hepatic	➢ Presinusoidal ○ Schistosomiasis ○ Congenital hepatic fibrosis ➢ Sinusoidal ○ Cirrhosis–many causes ○ Alcoholic hepatitis ➢ Post sinusoidal ○ Hepatic sinusoidal obstruction (veno-occlusive syndrome)

III. Post hepatic	➢ Budd-Chiari syndrome ➢ Inferior vena caval webs ➢ Cardiac causes: ○ Restrictive cardiomyopathy ○ Constrictive pericarditis ○ Severe CHF

9.1.1.2 Ascites

- Ascites is the accumulation of fluid within the peritoneal cavity.
- The most common cause of ascites is portal hypertension related to cirrhosis.
- However, malignant or infectious causes of ascites can be present as well, and careful differentiation of these other causes are obviously important for patient care. This can be differentiated by SAAG from Ascitic fluid analysis *(refer short case of nitsibin (click here →* **Ascitic fluid analysis***))*

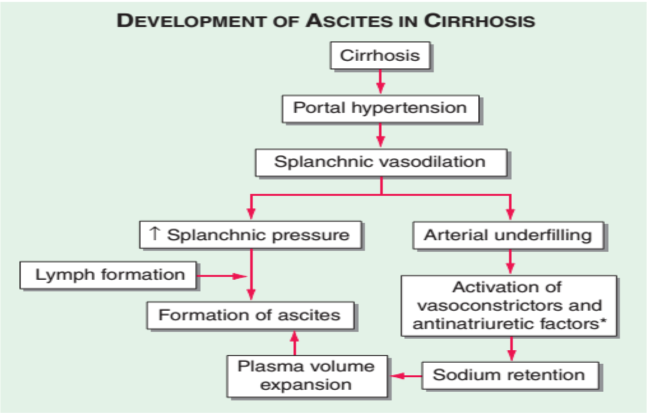

DEVELOPMENT OF ASCITES IN CIRRHOSIS
Cirrhosis
Portal hypertension
Splanchnic vasodilation
↑ Splanchnic pressure
Arterial underfilling
Lymph formation
Activation of vasoconstrictors and antinatriuretic factors*
Formation of ascites
Plasma volume expansion
Sodium retention

FIGURE 337-4 Development of ascites in cirrhosis. This flow diagram illustrates the importance of portal hypertension with splanchnic vasodilation in the development of ascites. *Antinatriuretic factors include the renin-angiotensin-aldosterone system and the sympathetic nervous system.

Management

- Salt restriction (< 2 g/day) (post at the bedside of the pt like this → ''salt free diet/ ጨው ክልክል'')
- See general management principles above

First line

- **Spironolactone**
  - Starting dose 100 mg/day daily or BID
  - If there is no response; increase doses every 3-7days (in 100 mg steps). Maximum dose 400mg/day
  - Serum potassium should be checked regularly: at start, at dose increments and on each follow up visit

Add- on or alternative

- **Furosemide**
  - Starting dose: 20mg, BID, Increments by 40mg/day. Maximum dose: 160 mg/day (80mg BID)
  - Ass add-on: in patients who do not respond to spironolactone (body weight reduction less than 2 kg in one week)
  - As an alternative: in patients who have hyperkalemia or impaired kidney function at baseline or develop later

N.B

- **Keep spironolactone to Lasix ratio of 5 : 2 to prevent hypokalemia since spironolactone is potassium sparing diuretic**
- **Spironolactone is preferred in ascites from CLD unlike other causes of ascites because of the following reasons**
  - **To prevent hypokalemia**
  - **To prevent dehydration from lasix (since loop diuretics like Lasix are strong diuretics which may cause dehydration. Hypokalemia and dehydration are precipitant of hepatic encephalopathy)**
  - **Loop diuretics are less effective in ascites from CLD because there is low albumin for their mechanism of action**
  - **RAAS is the cause of ascites in CLD**
- **loop diuretics like Lasix are strong diuretics and preferred in other causes of ascites like CHF, Nephrotic syndrome, AKI/CKD….**

- If ascites is still present despite the above measurements, it is defined as ***refractory ascites.***
- Alternative treatment modalities include:
  - large-volume paracentesis (**Therapeutic tap) for huge ascites;** Look at paracentesis and ascitic fluid analysis under short case of nitsibin (click here → Peritoneal tap (paracentesis))
  - TIPS (Trans jugular intrahepatic portosystemic shunt) procedure
  - Liver transplant

9.1.1.3 Spontaneous bacterial peritonitis (SBP)

- SBP is defined as a spontaneous ascitic fluid infection without an evident intra-abdominal source.
- It is common in patients who have low protein ascites (<1g/dL). i.e. Low ascitic fluid albumin level and advanced CLD are risk factor for SBP. This is because of albumin have opsonizing (protective) property.
- **Pathogenesis:** the source of infection is mostly hematogenous. Bacterial translocation from gut flora → mesenteric lymph nodes → bacteremia and infection of the ascitic fluid.
- It is a complication of Ascites in 8% of cases
- Etiologies:
  - *E. coli → most common cause*
  - *S. viridans*
  - *S. aureus*

- *Enterococcus* sp
- *Klebsiella*

- Clinical manifestations:
  - Fever
  - abdominal pain and tenderness
  - diarrhea
  - rarely worsening of jaundice and HE (altered mental status)
- Diagnosis:
  - Positive ascitic fluid bacterial culture and
  - ANC (Absolute neutrophil count) > 250 cells / µL

Bacterial peritonitis	
SBP	Secondary peritonitis due to rupture of abdominal viscus
➢ **WBC > 500/mm3 (neutrophil ≥ 50%)** ➢ **Mono microbial**	➢ **WBC > 10,000/mm3 (significant leucocytosis)** ➢ **Multiple organisms identified** ➢ Increased LDH level ➢ Glucose < 50 ➢ Protein significantly decreased ➢ PH ➢ With obvious cause of 2ry peritonitis like intestinal perforation ➢ Failure to improve after standard treatment with in 48 hr's

Spontaneous bacterial peritonitis variants that do not require surgery

Variant	Ascitic fluid culture	Absolute PMN per mm3
Classic SBP (Ascites + Mono bacterial infection + ANC ≥250)	Positive	≥250
Culture-negative neutrocytic ascites	No growth	
Monomicrobial non-neutrocytic bacterascites (single organism)	Positive	< 250
Polymicrobial bacterascites	Positive	

Treatment of SBP

First line:

- ✓ Ceftriaxone, 1g, IV, BID for 7-10 days

Alternative:

- ✓ Ciprofloxacin, 200mg, IV, BID for 7-10 days

Prophylaxis for SBP

- ➢ Indications to start prophylaxis
  - Patients who recover from an episode of SBP
  - Advanced cirrhosis and ascitic fluid protein <1.5 g/dl without prior SBP

- In patients with GI bleeding and severe liver disease

First line:

- ✓ Norfloxacin, 400mg, P.O. daily

Alternatives

- ✓ Cotrimoxazole (TMP-SMZ), 960mg PO, daily
- ✓ Ciprofloxacin 500mg PO, daily

- Duration of prophylaxis: Generally indefinite but if there is long-lasting improvement with disappearance of ascites, prophylaxis can be discontinued.

9.1.1.4 Esophageal varices and Variceal bleeding

- Screening studies have shown that approximately one third of patients with histologically confirmed cirrhosis have varices. Approximately 5 - 15% of cirrhotic patients per year develop varices.
- Varices develop in order to decompress the hypertensive portal vein and return blood to the systemic circulation
- Clinical feature
  - Signs and symptoms of CLD
  - Painless but massive hematemesis
  - Hypotension with/without shock
- Investigation
  - Emergency endoscopy
  - blood type and cross match
  - CBC, OFT, PT and PTT…

Approach to the management of variceal hemorrhage

- There are four major issues related to the prevention and treatment of variceal hemorrhage:
  - Prediction of patient at risk
  - Primary and pre-primary prophylaxis against variceal hemorrhage in patients with cirrhosis
  - Treatment of an active bleeding
  - Prevention of rebleeding

1) Predictive Factors for risk of variceal hemorrhage in patients with cirrhosis

- Location of varices
- Size of varices
- Appearance of varices
- Clinical features of the patient
- Variceal pressure

10) **Prevention of variceal bleeding (Both Pre-primary and Primary,** some expertise uses the term primary and secondary)

- Primary prophylaxis aims to prevent variceal hemorrhage in patients with esophageal varices who do not have a history of hemorrhage.
- Pre-primary prophylaxis refers to measures aimed at preventing the development of varices.
- These measures are aimed at achieving one of the following results:
  - **Decreasing portal hypertension**
    - ✓ beta blockers → **Propranolol, 20mg - 40mg, PO, BID or TID.** Start low dose and escalate gradually.
    - ✓ surgical portal decompression
    - ✓ TIPS (trans jugular intrahepatic portosystemic shunts) → functions like side-to-side surgical portocaval shunt, but does not require general anesthesia or major surgery for placement.
  - **Treating the varices directly**
    - ✓ **Endoscopic variceal band ligation**

11) Management of Active Bleeding

- There are three primary goals of management during the active bleeding episode:
  - i. Hemodynamic resuscitation
  - ii. Treatment of complications
  - iii. Treatment of bleeding

I. Hemodynamic resuscitation

- airway stabilization
- Blood loss should be replaced by packed cells and clotting factors should be replaced as needed If platelet is < 50,000/mm^3 in an actively bleeding patient
- Patients must be monitored carefully to avoid over transfusion with volume overload because of the risk of rebound portal hypertension and induction of rebleeding

II. Treatment of complications

- The principal complications that cause death are
  - Aspiration pneumonia
  - Sepsis
  - acute-on-chronic liver failure
  - hepatic encephalopathy, and
  - renal failure

III. Treatment of bleeding

Pharmacologic treatment

- Intravenous vasopressin and its analogs intravenous vasopressin directly constricts mesenteric arterioles and decreases portal venous inflow, thereby reducing portal pressure

- somatostatin and their analogs - Somatostatin inhibits the release of vasodilator hormones such as glucagon, indirectly causing splanchnic vasoconstriction and decreased portal inflow.

Endoscopic treatment

- endoscopic therapy can be done at the time of diagnosis and it’s the definitive treatment of choice for active variceal hemorrhage
- There are two forms of endoscopic treatment
    - Sclerotherapy involves injection of a sclerosant solution into the varices through an injection needle
    - Variceal band ligation involves placing small elastic bands around varices in the distal 5 cm of the esophagus
- Balloon tamponade → is an effective way to achieve short-term hemostasis, but due to complications and rebleeding upon balloon deflation, its use is reserved for temporary stabilization of patients until more definitive treatment can be instituted.

IV. Prevention of Rebleeding

- Band ligation
- Non selective beta blockers
- Beta blockers plus band ligation → Combination therapy with a beta blocker plus endoscopic band ligation is more effective at preventing rebleeding than band ligation alone or beta blockers alone.

9.1.2 Hepatic insufficiency related CXN

9.1.2.1 Hepatic Encephalopathy (HE)

- Hepatic Encephalopathy is an alteration in mental status and cognitive function occurring in the presence of liver failure.
- It is potentially reversible neuropsychiatric abnormality
- Pathogenesis
    - Gut derived neurotoxins → Porto systemic shunt of nitrogenous chemicals (e.g. NH_3) which are toxic to brain
    - Hepatic insufficiency → liver failed to detoxify NH_3 and other neurotoxic chemicals
    - False neurotransmitters and mercaptans
    - Ammonia level is typically elevated in HE patients
- Look at clinical features of HE from CLD hx section above

Precipitating Factors

- Dehydration and Hypovolemia

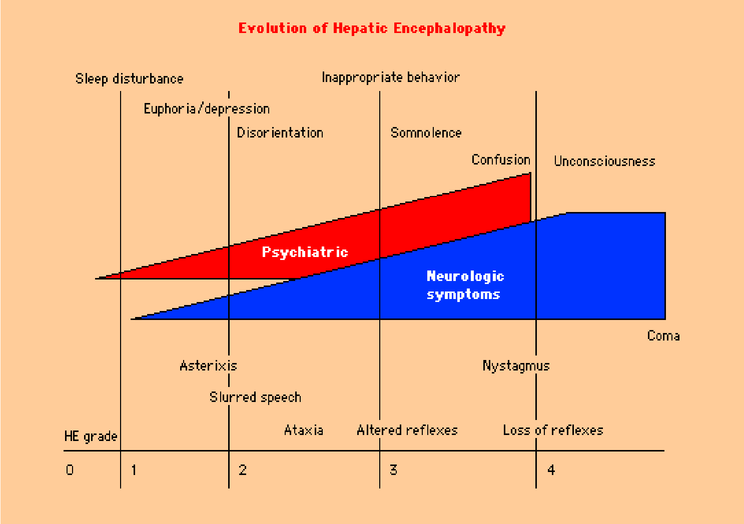
- Electrolyte imbalance (e.g. hypokalemia)
- GI bleeding → increase ammonia production
- Infections (e.g. SBP)
- Hypoglycemia
- High protein diet → increased nitrogenous chemical n production by colonic bacteria
- Constipation
- Hypoxia
- Sedatives

Clinical Assessment

- Signs and symptoms suggesting of Precipitating factors
- Clinical scale for assessment of hepatic encephalopathy
    - **Modified West Haven criteria (0–4)**
    - Sonic (unimpaired, covert, overt)

Clinical grading of HE (Modified West Haven criteria)

Clinical grade	Signs	Flapping tremor
Grade I (Prodrome)	➢ **Alert, slow mentation** ➢ **Reversed sleep awake pattern** → sleep in the day and awake at night ➢ Euphoric, occasionally depression, poor concentration, slow mentation and affect	Infrequent
Grade II (Impending coma)	Lethargy, drowsy, personality changes, disorientation	Easily elicited
Grade III (early coma)	Stupor but easily arousable, incoherent speech, Marked confusion	Usually present
Grade IV (deep coma)	Coma, unresponsive but may response to painful stimulus	Usually absent


Evolution of Hepatic Encephalopathy
Sleep disturbance
Inappropriate behavior
Euphoria/depression
Disorientation
Somnolence
Confusion
Unconsciousness
Psychiatric
Neurologic symptoms
Coma
Asterixis
Nystagmus
Slurred speech
Ataxia
Altered reflexes
Loss of reflexes
HE grade
0
1
2
3
4

Management of HE

Management principles

- supportive care
- Treatment of precipitating factors
- Treatment of concomitant cause of encephalopathy
- Specific treatment for HE

Supportive Care

- Patients that exhibit grade 3 or higher HE should be transferred to ICU
- Provision of nutrition for the unconscious
- Provision of oxygen
- Frequent positioning

Treatment of precipitating factors

- Correction of dehydration
- Correction of electrolyte imbalance
- Treatment of infection
- Control of GI bleeding
- Dietary protein management → **In the past, restriction of dietary protein was considered for patients with encephalopathy; however, the negative impact of that maneuver on overall nutrition is thought to outweigh the benefit when treating encephalopathy, and it is thus discouraged.** There may be some benefit to replacing animal-based protein with vegetable-based protein in some patients with encephalopathy that is difficult to manage.

Treatment of concomitant cause of encephalopathy

- Concomitant cause of encephalopathy and HE are diagnosed and treated at the same time (e.g. Sepsis, hypoglycemia)

Provision of specific treatment for HE

- **Lactulose**
  - A non-absorbable disaccharide which results in colonic acidification
  - The usual dosage is **10 - 30mL PO** (Via NG tube) **TID.**
  - **The goal of lactulose is to promote 2-3 soft stools per day** and no diarrhea
  - **Dose for Overt hepatic encephalopathy episodes, treatment:**
    - ✓ Route not specified: 16.7 g (25 mL) every 1 to 2 hours until at least 2 soft or loose bowel movements are produced daily; titrate to maintain 2 to 3 bowel movements daily.
  - **Dose for Subclinical (minimal) hepatic encephalopathy:**

  - ✓ 20 to 40 g (**30 to 60 mL) daily in 2 to 3 divided doses to maintain 2 to 3 bowel movements daily** for up to 3 months

PLUS

- **Metronidazole**, 250mg, PO, TID, for 5 to 10 days **or**
- **Neomycin,** 4 to 12 g daily divided every 4 to 6 hours for 5 to 6 days
  - **For Chronic hepatic insufficiency:** 4 g PO daily for an indefinite period

  or
- **Rifaximin,** 400 mg PO TID, for 5 to 10 days

PLUS

- **Zinc supplementation**

9.1.2.2 Hepatorenal Syndrome (HRS)

- HRS usually represents the end stage of sequence of reduction in renal function induced increasingly by severe hepatic injury.
- It's is a firm of functional renal failure without renal pathology.
- It occurs in 10% of patients with advanced liver disease and Acute Liver Failure.
- **HRS is a diagnosis by exclusion** w/c is characterized by:
  - progressive rise in serum creatinine
  - a benign urine sediment
  - no or minimal proteinuria
  - low rate of sodium excretion(<10meq/l)
  - oliguria in a Patient who has established acute or chronic liver disease

Types of HRS

- Type 1 HRS
  - more serious type
  - 2X increase serum creatinine to a level > 2.5 mg/dl within 2 wks
- Type2 HRS
  - decreased GFR with an increase in serum creatinine but is fairly stable and with better outcome
  - major feature is ascites that is resistant to diuretics

Precipitants

- Onset of HRS is typically gradual but it Can be precipitated by:
  - bacterial infection E.g. SBP
  - GI bleeding

Pathogenesis

- arterial vasodilation in splanchnic circulation due to portal HTN → Nitric oxide (No): most important vasodilator

Diagnosis: based on clinical criteria

- No specific test to establish diagnosis
  - HRS Should be considered after exclusion of other potential cause
- The following **diagnostic criteria** is proposed for HRS
  - Chronic or acute hepatic disease with advanced hepatic failure and portal HTN
  - Sr. Creatinine > 1.5 gm/dl progressing over days to wks
  - absence of any apparent cause of AKI but the presence of another renal diagnosis (e.g. diabetic nephropathy) does not necessarily exclude HRS

Treatment

- Ideal therapy is improvement of liver function. However, when patient is not responding in short term, medical therapy is recommended
  - In ICU pts: norepinephrine + albumin
  - In non-ICU pts: based on availability of drugs
- In highly selected pts, who fail to respond to medication: Trans jugular intrahepatic Porto systemic shunt (TIPS)
- Patients who fail to respond, develops severely impaired renal function and may need liver transplant or may recover if liver injury is reversible (dialysis as a bridge is recommended)

Prevention

- HRS regularly develops in pts with SBP or severe alcoholic hepatitis. The following therapies may Prevent development of HRS
  - IV albumin
  - Norfloxacin
  - pentoxifylline

Prognosis

- overall mortality of pts. with liver-failure is substantially worse if they develop HRS
- without therapy most pts die within wks of onset of renal impairment

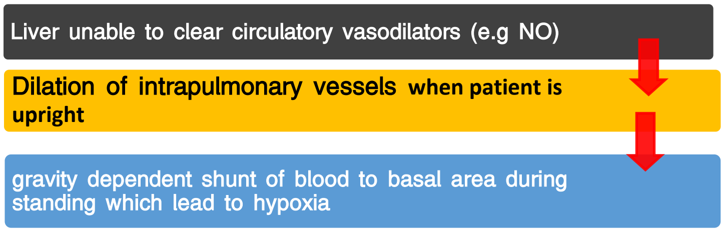
9.1.2.3 Hepatopulmonary syndrome (HPS)

- HPS is considered **when the following triad** exists:
  i. **Liver disease**
  ii. **Impaired oxygenation**
    - most sensitive measure being alveolar-arterial(A-a) O_2 gradient > 15 mm Hg. Also, Pa02 < 80 mm Hg
    - For pts > 65 year - A-a gradient > 20 mm Hg, Pa O_2 < 70 mm Hg
  iii. **Intrapulmonary vascular abnormality**
    - referred to as intrapulmonary Vascular dilatation (IPVD). IPVD can be diagnosed by contrast echo, nuclear scanning or pulmonary angiography
- The unique Pathological feature of HPS is gross dilatation of pulmonary precapillary and capillary vessels

- It's Mostly associated with portal HTN
- Prevalence: 4 - 47% (depend on diagnostic criteria)
- Other test: CXR, HRCT, PFT

Clinical manifestation of HPS

- Consequence of both hepatic & Pulmonary dysfunction
- More than 80% present with smx of liver disease. The remaining 20% present with dyspnea as 1st manifestation but not specific to HPS (it can be due to hepatic hydrothorax, Porto Pulmonary HTN, anemia, ascites…Etc.)
- **Platypnea and orthodeoxia rather are more specific for HPS**
    - Platypnea (dyspnea in upright position) is an increase in dyspnea induced by moving into an upright position and relieved by recumbency
    - orthodeoxia is a decrease in arterial O2 tension (by > 4 mm Hg) or desaturation (by > 5%) when pt moves from supine to up right.
    - If they coexist together it is called **platypnea-orthodeoxia SXX**
- What is the mechanism of platypnea?


Liver unable to clear circulatory vasodilators (e.g NO)
Dilation of intrapulmonary vessels when patient is upright
gravity dependent shunt of blood to basal area during standing which lead to hypoxia

Treatment

- No effective medical therapy
- Rather supplemental O_2 and liver transplantation have promising out come

Prognosis

- Prognosis of Pt with HPS is worse than that of cirrhosis pt without HPS (median survival is 24 months for pt with HPS and 5 yr Survival is only 23% while pt without HPS have 5 yr survival of 63% & median Survival of 87months).
- But with liver transplantation survival is comparable.

9.1.2.4 Synthetic dysfunction

A. Hypoalbuminemia

B. Coagulopathy in liver disease

- Clotting process is a dynamic aggregation of multiple process, which can be Viewed as occurring in 4 phases:
  - initiation & formation of Platelet plug
  - Propagation of clotting by coagulation cascade
  - Termination of clotting by antithrombin
  - Removal of clot
- Liver is responsible for production of almost all protein including coagulation factors except factor8.
- In patient with liver disease there is rebalanced hemostasis. therefore, either an increased risk of bleeding as well as thrombosis.
- Coagulation abnormality can be Hypocoagulability or Hypercoagulability.
- Hypocoagulability → increased bleeding risk
  - decreased production of coagulation factors
  - Abnormalities of platelet number and function
  - Mechanism → decreased hepatic synthesis of thrombopoietin, bone marrow suppression (e.g. HCV infection, alcohol use) or hypersplenism
  - infection and endogenous heparinoids
  - hyperfibrinolysis
- Hypercoagulability → increased thrombotic risk
  - decreased production of natural anticoagulant (macro thrombi, micro thrombi)

Tests of coagulation in liver disease

- PT, aPPT and INR
- Platelet level and function: bleeding time
- Fibrinogen and individual factor levels
- Fibrin degradation product and D-dimer
- Thrombin generation testing
- Thromboelastography and thromboelastometry
- Sonorheometry

Treatment of bleeding

- Proper treatment requires answers to the following questions
  - Any comorbidity presents?
  - Is vit k deficiency present (more likely in primary cholestatic diseases)?
  - Is DIC present?
  - Is platelet count adequate?
  - What is the status of fibrinogen and is fibrinolysis present?
  - Is there danger of volume overload?
  - Is there oral mucosal bleeding w/c can be corrected by antifibrinolytics?

Prevention and treatment of thrombosis

- Venous thromboembolism prophylaxis in hospitalized patients
- Antiplatelet and anticoagulant therapy

9.2 Causes of CLD

- There are various disorders that cause CLD (look at DDX above)
- We will discuss some of the causes here (viral hepatitis, alcoholic liver disease, autoimmune hepatitis, Wilson disease, hemochromatosis, AAT deficiency, NAFLD and NASH)

9.2.1 Viral Hepatitis (ሄፓታይቲስ ቫይረስ እና የጉበት ብግነት)

- Viral hepatitis is a systemic infection affecting the liver predominantly.
- Almost all cases of viral hepatitis are caused by one of five viral agents: HAV, HBV, HCV, the HBV-associated delta agent or HDV, and HEV.
- All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus but replicates like a retrovirus.
- Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses.
- These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive CLD with cirrhosis and even HCC, common to the bloodborne types (HBV, HCV, and HDV), on the other.

Table; hepatotropic viruses						
Virus		HAV	HBV	HCV	HDV	HEV
Group		Enterovirus	Hepadnavirus	Flavivirus	Delta particle	(incomplete virus)
DNA/RNA		RNA	DNA	RNA		
Size		27 nm	40-42 nm	30-35 nm	35 nm	27 nm
Remarks		called infectious hepatitis	called serum hepatitis	previously called non - A non - B, now HCV	defective RNA virus; needs HBV to infect	
Spread	**Faeco-oral**	Yes	NO			Yes
	Blood	Uncommon	Yes			
	Saliva	Yes			-----	
	Sexual	Uncommon	Yes	Uncommon	Yes	Uncommon
	Vertical	No	Yes	Uncommon	Yes	No
Chronic infection	Incidence	Not known	5-10%	>50%	-----	
	Severity	Mild	Often severe	Moderate	Unknown	Mild to moderate
Prevention	Active	Vaccine	Vaccine	No	? Prevented by HBV infection	No
	Passive	serum globulins			No	

Antigen	HAV Ag	HBsAg, HBcAg, HBeAg	HCV Ag	HBsAg, HDV	HEV Ag
Antibody	Anti- HAV	Anti- HBsAg, Anti- HBcAg, Anti- HBeAg	Anti- HCV	Anti- HBsAg, Anti- HDV	Anti- HEV
Prognosis	Good	Worst with age	Moderate	Same as with Good	

- Non hepatotropic viruses (viruses that indirectly affect the liver) include; EBV, CMV, HSV, measles, Ebola, & others
- Viral hepatitis can be;
  - **Acute viral hepatitis or**
  - **Chronic viral hepatitis**

Acute viral hepatitis

- It is defined by the sudden onset of significant aminotransferase elevation as a consequence of diffuse necro inflammatory liver injury. Symptoms may be variable. This condition may resolve or progress to fulminant failure or chronic hepatitis.

Acute Liver Failure and Fulminant Hepatitis

- **Acute liver failure (ALF)** refers to the rapid development of **severe acute liver injury with impaired synthetic liver function and hepatic encephalopathy** in a person who **previously had a normal liver** or well-compensated liver disease.
- **Fulminant hepatitis (FH)** refers to the development of **hepatic encephalopathy within 8 weeks of the onset of symptoms in a patient with a previously healthy liver** or the appearance of **encephalopathy within 2 weeks of developing jaundice.**
- Causes of ALF or FH are similar to that of acute hepatitis.
- **Clinical features;** Jaundice, Bleeding, Ascites and edema, Hepatic encephalopathy, Decreased urine out put

Treatment

- Patients should be treated in an ICU setting.
- Secure air way, IV line, correct hypoglycemia and hypotension, insert NG tube if unconscious
- If you are in primary hospital, Catheterize the urinary bladder and refer to a referral hospital with ICU facilities.

Chronic hepatitis

- is defined as the presence of persistent (at least 6 months) necro inflammatory injury that can lead to cirrhosis.
- Persistently abnormal serum transaminase levels and characteristic histologic findings.
- We can classify chronic hepatitis based on its etiologic, histologic activity(grade) and degree of progression/stage.
- Etiologic → Chronic viral hepatitis (most common cause of CLD) which include; HBV, HBV and HDV coinfection, HCV
- Grade: histologic assessment of necro inflammatory activity.
    - Mild
    - Moderate
    - Severe
- By stage: degree of fibrosis
    - Stage 0 = no fibrosis
    - Stage 1 = mild fibrosis
    - Stage 2 = moderate fibrosis
    - Stage 3 = severe fibrosis
    - Stage 4 = cirrhosis

Hepatitis B Virus infection

- Hepatitis B virus (HBV) is a double-stranded hepatotrophic DNA virus.
- HBV infection is a global health problem.
- The prevalence of HBV is highest in sub-Saharan Africa and East Asia.
- Though there is no a nationwide epidemiology study, several studies indicate that Ethiopia has a high burden of HBV infection.
- HBV is transmitted by percutaneous or mucosal exposure to infected blood or body fluids (saliva, menstrual, vaginal, and seminal fluids).
- Mother to child (perinatal) transmission is an important route of transmission.
- Transmission within a household, particularly to children is also an important contributor.
- Sexual transmission may occur in those with multiple sex partners.
- The risk of developing chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20 - 60% between the ages of 6 months and 5 years. Infection in adulthood leads to chronic hepatitis in < 5% of cases
- HBV infection causes a number of clinical problems: acute hepatitis, chronic hepatitis, liver cirrhosis, HCC, and extrahepatic features (e.g. glomerulonephritis, vasculitis)
- Liver cirrhosis and HCC are the two major causes of death in patients with chronic HBV infection
- Chronic HBV infection is a dynamic process due to viral replication and the host immune response.
- viral replication status (HBeAg status), HBV DNA level (viral load), ALT values and status of liver inflammation, HBV infection is divided into five phases. (see the table 2 below)

- Having evidence of HBV infection does not necessarily indicate liver injury (hepatitis) or the consequences of liver injury (liver cirrhosis and HCC).
- The presence of liver injury (hepatitis) is confirmed by a rise in transaminases (mainly ALT) or imaging/clinical evidence of liver fibrosis and cirrhosis. (for terminologies see table 1 below)

Table1. Important terminologies in the natural history of HBV infection	
Acute HBV infection	➢ New-onset hepatitis B infection that may or may not be symptomatic. ➢ Diagnosis is based on detection of HBsAg and IgM antibodies to hepatitis B core antigen (anti-HBc).
Chronic HBV infection	Persistence of HBsAg for ≥ **6 months** after acute infection with HBV.
HBeAg seroconversion	Loss of HBeAg and development of anti-HBe antibody
HBsAg seroconversion	Loss of HBsAg and development of anti-HBs
HBeAg reversion	Reappearance of HBeAg in a person who was previously HBeAg negative
Cirrhosis	➢ An advanced stage of liver disease as evidenced by imaging or biopsy. Characterized by: o Extensive hepatic fibrosis o Nodularity of the liver and alteration of liver architecture
Decompensated cirrhosis	Clinical complications of cirrhosis become evident o Jaundice o Ascites o SBP o Esophageal varices and bleeding o Hepatic encephalopathy o Renal impairment

Diagnosis and diagnostic evaluation

- The diagnosis of HBV infection starts with HBsAg. If +ve do the IX listed under Ix section above
- In addition to those suspected of having liver disease, certain group of individuals need **routine screening with HBsAg.**
    - Pregnant mothers
    - Infants born to infected mothers
    - Health care workers (including health professionals and supporting staff)
    - Hemodialysis patients and organ transplant recipients
    - People with multiple sexual partners and I.V drug users
    - Sexual partners of infected individuals
    - HIV or HCV positive patients

Table 2. Phases of chronic HBV infection

			HBsAg	HBeAg	HBV DNA	ALT	Liver disease (fibrosis or cirrhosis)	Previous (Old) terminology
HBeAg positive	**phase 1**	HBeAg +ve chronic HBV infection with no evidence of current hepatitis	Positive		high (usually $>10^7$ IU/ml)	normal	None to mild	Immune tolerant
	phase 2	HBeAg +ve chronic HBV hepatitis			high (10^4 - 10^7 IU/ml)	Elevated (persistently or intermittently)	present (moderate or severe)	Immune reactive HBeAg positive
HBeAg Negative	**phase 3**	HBeAg -ve chronic HBV infection with no evidence of current hepatitis	Positive	Negative	low (<2,000 IU/ml) or undetectable	Normal	None	Inactive carrier
	phase 4	HBeAg -ve chronic HBV hepatitis			high (>2,000 IU/ml)	Elevated (persistently or intermittently)	Present (moderate or severe)	HBeAg negative chronic hepatitis
HBsAg-negative phase	**phase 5**		Negative		HBV antibodies = +ve anti-HBcAg with or without anti-HBsAg.	Normal	None	occult HBV infection

Follow up tests

- In patients with chronic HBV but no indications for antiviral therapy, liver injury as well as viral replication can be variable; hence, regular monitoring is required.
    - ALT, APRI score, clinical evaluation every 3 months in all patients
    - **HBeAg initially negative:** HBeAg and HBV DNA level every 6 -12 months
    - **HBeAg positive initially**: HBV DNA level every 6 -12 months

Treatment

Objectives of treatment

The main objectives of HBV treatment

- Reduce progression to cirrhosis, HCC and associated mortality
- Improve liver fibrosis
- Preventing acute or subacute liver failure in acute HBV infection
- Controlling extrahepatic manifestations.
- Prevention of HBV reactivation.
- Prevention of mother to child transmission.

Intermediate objectives of treatment

- Suppression of HBV DNA levels
- Induction of HBeAg loss, with or without anti-HBe seroconversion
- Biochemical response; ALT normalization
- HBsAg loss: optimal goal but rarely achievable

Pharmacologic treatment

- Patients with HBsAg positivity with or without elevated transaminases or evidence of CLD need evaluation for indications of therapy i.e. HBeAg status, HBV DNA level

Indications for antivirals in chronic HBV infection.

- Indications are determined based on the presence or absence of cirrhosis, APRI score (see IX section above), ALT, HBV DNA level, and HBeAg.
- The following are the indications
  - All patients with **cirrhosis (decompensated)** and **any detectable viral load**: Irrespective of ALT and HBeAg status.
  - If no liver cirrhosis, one of the following is an indication for antiviral treatment
    - ✓ **HBV DNA > 20,000 IU/ml and elevated ALT** (above the UNL): Irrespective of HBeAg status
    - ✓ **Detectable HBV DNA and APRI score ≥ 2 or elevated ALT** (above UNL): Irrespective of HBeAg status
    - ✓ **Age above 30, HBeAg-positive and HBV DNA > 2,000**: Irrespective of ALT
    - ✓ **Co-infection with HIV.**
    - ✓ Patients **with chronic HBV to be started on immunosuppresses.**
    - ✓ **Extra hepatic manifestation**

Indications for antiviral in acute HBV infection

- The presence **acute liver failure or fulminant hepatitis with detectable HBV DNA.**

Antiviral choices

First line

- ✓ **Tenofovir** (Tenofovir disoproxil fumarate) **(TDF) 300mg, PO, daily**
    - Avoid in patients with GFR <60ml/min

OR

- ✓ **Entecavir 0.5mg, PO, daily.**
    - For patients with **decompensated cirrhosis or those with previous exposure to Lamivudine** the dose should be increased to **1mg, daily**.
    - Entecavir is **preferred** over Tenofovir in patients **age > 60, CKD, osteoporosis or steroid use.**

Alternatives

- ✓ **Telbivudine 600mg, PO, daily.**
    - It should only be used when both first lines are not available or in patients with renal impairment when Entecavir is not available.

Monitoring treatment response

- HBV DNA: every 3 months until undetectable then every 6 months.
- ALT: every 3 months.
- HBeAg and antibody to HBeAg (anti-HBe): every 6 months in patients who are HBeAg-positive.
- Monitoring side effects of tenofovir: serum creatinine and phosphate every 3-6 months.

Duration of antiviral therapy

- Most patients require indefinite treatment
- For patients with cirrhosis treatment should be continued indefinitely.
- For patients without cirrhosis: HBeAg seroconversion to negative and development of HBeAb, if initially HBeAg is positive is considered as possible endpoint of treatment.
- For patients without cirrhosis and initially HBeAg is negative, it’s only loss of HBsAg which is considered an endpoint but it happens very rarely; hence, treatment is generally indefinite.

Treatment in special population

HBV/ HIV co-infection

- HIV co-infection profoundly affects almost every aspect of HBV infection and includes more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV co-infection

- HIV/HBV-co-infected persons also demonstrated rapid HIV disease progression compared to HIV-infected alone, and had an impaired recovery of CD4 cells.
- HIV patients are among the high-risk groups for HBV and should be given priority for screening. i.e. all HIV patients should get screened for HBV and evaluated for chronic infection.

Treatment options

- ART should be initiated in all HIV patients regardless of WHO staging or CD4 count in individuals co-infected with HIV and HBV with evidence of severe CLD.
- If HBV treatment is indicated among HBV/HIV co-infection, combination ART should be initiated with drugs containing **TDF + 3TC (or FTC) + EFV** as a preferred regimen.
- Use of lamivudine as mono-therapy in any of these diseases is contraindicated due to high resistance.
- When switching treatment in patients with HIV on ART failure, the regimen that will continue should have two of the drugs having activity against HBV.
- If tenofovir-associated renal toxicity occurs, the dose of tenofovir should be adjusted according to the renal clearance.

HCV coinfection:

- Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV.
- Patients fulfilling the standard criteria for HBV treatment should receive treatment.
- HBsAg-positive patients undergoing HCV treatment with DAA therapy should be given concomitant treatment.

Pregnancy:

- In all pregnant women with high HBV DNA levels >200,000 IU/ml Tenofovir (TDF) should be started at 24 - 18 weeks of gestation and continue for up to 12 weeks after delivery.
- Pregnant women already on NA therapy, Tenofovir should be continued, if on another agent it should be switched to Tenofovir.
- Tenofovir is not contraindicated in breast feeding.

HBV vaccination in adults

Indications for vaccination

- Healthcare workers
- Immune-compromised individuals including HIV
- Organ transplant recipients
- Patients on maintenance hemodialysis
- Children 1-5 years who missed immunization for HBV

- Sexual partners and close contacts of infected individuals receive three doses of HBV vaccine.

Vaccination schedule

- ✓ Standard schedule: 0, 1, and 6 months.
- ✓ Accelerated schedule: 0, 1 and 2 months.
  - Accelerated schedule, if requested for rapid protection within 48 hours of exposure: 0, 7 and 21 days.
  - After an accelerated course, a booster at one year is recommended.

HBV Immunoglobulin

- HBV immunoglobulin provides passive immunity
- Indications: In individuals who have not been immunized or have not completed the immunization and have the one of the following indications
  - **Perinatal exposure of an infant born to a HBsAg positive mother within 24 hours.**
  - Percutaneous or mucosal exposure to HBsAg-positive blood preferably within 24-48 hr.
  - Sexual exposure to an HBsAg-positive person

Hepatitis C virus infection

- HCV is a small, RNA-enveloped virus with a highly variable genome.
- It has multiple genotypes and sub genotypes. There are currently 7 genotypes identified with variable geographic distribution
- HCV is prevalent in Ethiopia and the commonest genotypes are genotype 4 (60%), followed by genotype 1 (20%).
- **Risk factors** for acquiring HCV: blood transfusion, IV drug use, cut or injury by bloody object, ear piercing or tattooing
- HCV can cause acute and chronic hepatitis, liver cirrhosis, and HCC.
- HCV can also cause a number of extrahepatic manifestations: Glomerulonephritis, vasculitis, thyroiditis, Sjogren syndrome, increase diabetes, porphyria cutanea tarda and lichen planus.
- Male gender, age above 40 or advanced age during infection, alcohol intake, HBV or HCV coinfection, fatty liver and obesity increase the risk of liver cirrhosis.

Diagnosis and investigation

Whom to screen for HCV?

- Pregnant women
- Patients with liver disease
- Individuals with HBV and HCV infection
- Commercial sex workers and prisoners
- Individuals with risk of acquiring infection (e.g. IV drug use, tattooing, body piercing)

Screening test

- Serum anti-HCV antibody rapid test or enzyme immunoassay EIA (ELISA)
- In the case of suspected acute hepatitis C, in immunocompromised patients and in patients on hemodialysis, HCV RNA testing can be done as an initial test.

Confirmatory test

- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method with a lower limit of detection ≤15 IU/ml) to confirm the diagnosis.
- If anti-HCV antibody-positive, but HCV RNA-negative individuals, HCV RNA levels should be repeated after 6 -12 months, to confirm past infection.

Investigations before initiation of treatment

- CBC, Liver enzymes and function test (AST, ALT, ALP, Bilirubin, ALB and INR), Serum Creatinine, BUN
- Quantitative HCV RNA (IU/ml)
- Prégnancy test for reproductive Age group women.
- HIV and HBV screening
- Other tests; see IX section above

Treatment

- All patients with HCV should be offered treatment. Those with liver disease or extrahepatic manifestations should be treated more urgently.

Objectives of treatment

- To eradicate HCV RNA (attainment of a sustained virologic response (SVR)).
- SVR is defined as an undetectable HCV RNA level after 12 weeks of therapy.

Who should be treated with direct acting antivirals (DAA)?

- All patients with HCV infection, who are willing to be treated, should be treated.
- Treatment should be started without delay in patients with significant fibrosis or cirrhosis, including decompensated cirrhosis; patients with clinically significant extra-hepatic manifestations.

Which agent to use?

- A simplified, pangenotypic anti-HCV treatment is preferred.
- Pre-treatment assessment can be limited to proof of HCV.

First line pangenotypic regimen

- ✓ **Sofosbuvir/velpatasvir** combination (400 mg of sofosbuvir and 100 mg of velpatasvir), **one tablet, daily for 12 weeks.**

Alternative regimen

- ✓ **Sofosbuvir** 400 mg, PO, daily plus **Daclatasvir 60mg PO,** daily for 12 weeks or
- ✓ **Sofosbuvir** 400mg, PO, daily plus **Ledipasvir** 90mg, PO, daily for 12 weeks.

○ For cirrhotic patient duration will be extended to 24 weeks for above treatment options.

OR

- ✓ **Sofosbuvir** 400mg, PO, daily plus **Ribavirin** 1g (weight < 75kg), 1200mg (weight ≥ 75Kg) twice on divided doses for 24 weeks.

Treatment monitoring

- HCV RNA at baseline, at the end of therapy (12 weeks) and after completion of treatment.
- Toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored.

HCV/HIV co-infection

- HIV patients are among high risk groups for HCV. Therefore, all HIV patients should be screened and confirmation Viral load test should be done for HCV screened positives
- All chronic HCV infected individuals should be treated to eradicate the virus and achieve cure so that complications can be avoided.
- Follow up quantitative or qualitative HCV RNA viral load is required to confirm if the patient has achieved Sustained Virologic Response (SVR). This should be performed 12 weeks after the completion of therapy.
- Treatment of HCV in HIV infected individuals is not different from non-HIV infected or HCV mono-infected. In case of Sofosbuvir + Daclatasvir combination, **dose of Daclatasvir be adjusted to 90 mg with Efavirenz and 30 mg with Atazanavir/r instead of 60mg dose of non RVI patients**

9.2.2 Alcoholic liver disease

- Chronic and excessive alcohol ingestion is one of the major causes of liver disease.
- The pathology of alcoholic liver disease consists of 3 major lesions, with the injury rarely existing in a pure form:

1. **Fatty Liver** → present in >90% of binge and chronic drinkers

2. **Alcoholic Hepatitis** → less common (10 - 20% of alcoholics) but precursor to cirrhosis. alcohol is considered a direct hepatotoxin which involves the complex interaction of facilitating factors, such as **Amount and frequency of intake**, **diet**, and **gender**. (see risk factor section of CLD above)

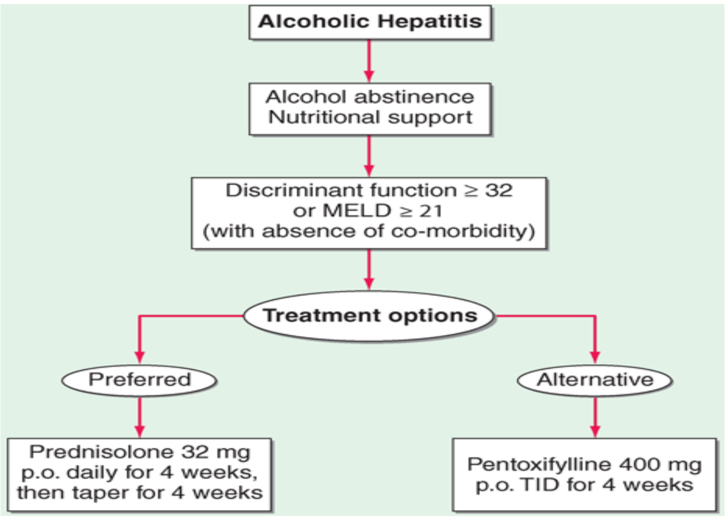
3. **Cirrhosis**

- The transition between fatty liver and the development of alcoholic hepatitis is blurred. **In fatty liver stage, cessation of drinking results in normalization of hepatic architecture and fat content within the liver.**
- Clinically, Differentiation of alcoholic fatty liver from nonalcoholic fatty liver is difficult unless an accurate drinking history is ascertained
- **Alcoholic hepatitis** is thought to be a precursor to the development of cirrhosis. *However, like fatty liver, it is* ***po tentially reversible with cessation of drinking.***
- ***Cirrhosis*** *is present in up to 50% of patients with biopsy-proven alcoholic hepatitis and its* ***regression is uncertain, even with abstention*** *of alcohol.*
- Chronic infection with HCV is an important comorbidity in the progression of alcoholic liver disease to cirrhosis in chronic and excessive drinkers.
  - Even moderate alcohol intake of 20 - 50 g/d increases the risk of cirrhosis and HCC in HCV-infected individuals.
  - Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival.

Management

- Complete abstinence from alcohol is the cornerstone in the treatment of alcoholic liver disease.
- nutritional and psychosocial support
- **glucocorticoids** have been extensively evaluated in the treatment of alcoholic hepatitis
  - Patients with severe alcoholic hepatitis *should be given prednisone, 32 - 40 mg/d, for 4 weeks, followed by a steroid taper*
  - Women with encephalopathy from severe alcoholic hepatitis may be particularly good candidates for glucocorticoids
  - Exclusion criteria include **active GI bleeding**, **renal failure**, or **pancreatitis.**
- **alternative** to glucocorticoids for severe alcoholic hepatitis.
  - **nonspecific TNF inhibitor**s (e.g. **pentoxifylline)**

Treatment algorithm for alcoholic hepatitis


Alcoholic Hepatitis
Alcohol abstinence
Nutritional support
Discriminant function ≥ 32
or MELD ≥ 21
(with absence of co-morbidity)
Treatment options
Preferred
Alternative
Prednisolone 32 mg
p.o. daily for 4 weeks,
then taper for 4 weeks
Pentoxifylline 400 mg
p.o. TID for 4 weeks

Prognosis

- Critically ill patients with alcoholic hepatitis have short-term (30-day) mortality rates >50%.
- The mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years
- The presence of *Ascites, Variceal hemorrhage, Deep encephalopathy, or Hepatorenal syndrome* Predicts a dismal prognosis.

9.2.3 Autoimmune hepatitis

- Autoimmune hepatitis is a chronic disorder of unknown etiology characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which can progress to cirrhosis and liver failure.
- Affects women more than men (3.6:1)
- Characteristics include: *Presence of autoimmune antibody*, *Evidence of hepatitis*, *Elevation of serum globulins*
- The prominence of extrahepatic features of autoimmunity as well as sero immunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis;
- Autoantibodies and other typical features of autoimmunity, however, do not occur in all cases;
- Among the broader categories of "idiopathic" or cryptogenic chronic hepatitis, many, perhaps the majority, are probably autoimmune in origin.
- The immune pathogenesis is Unknown, but assumed to be the result of a cell mediated immunologic attack directed against liver cells.
- Genetically predisposed individual with exposure to an environmental agent triggers the autoimmune pathogenic process.
- Overlap syndromes include; Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Chronic Hepatitis C.

Classification

I. Type I autoimmune hepatitis

- *It Is the classic syndrome occurring in young women.*
- ANA or Anti-Smooth Muscle antibody positive (*Titer usually > 1:100)*
- Bimodal age distribution (ages 10-20 and 45-70)
- Female : Male ratio = 3.6 : 1
- Associated with extrahepatic manifestations: *Autoimmune thyroiditis, graves' disease, chronic Ulcerative Colitis. Less commonly with RA, pernicious anemia, systemic sclerosis, ITP, SLE*
- 40% present with acute onset of symptoms similar to toxic hepatitis or acute viral hepatitis

☛ **Type II autoimmune hepatitis**

- *Often seen in children*
- *It Is not associated with ANA.*

III. Type III autoimmune hepatitis

- *These patients lack ANA*
- *Most of these patients are women and have clinical features similar to, perhaps more severe than, those of patients with type I autoimmune hepatitis.*

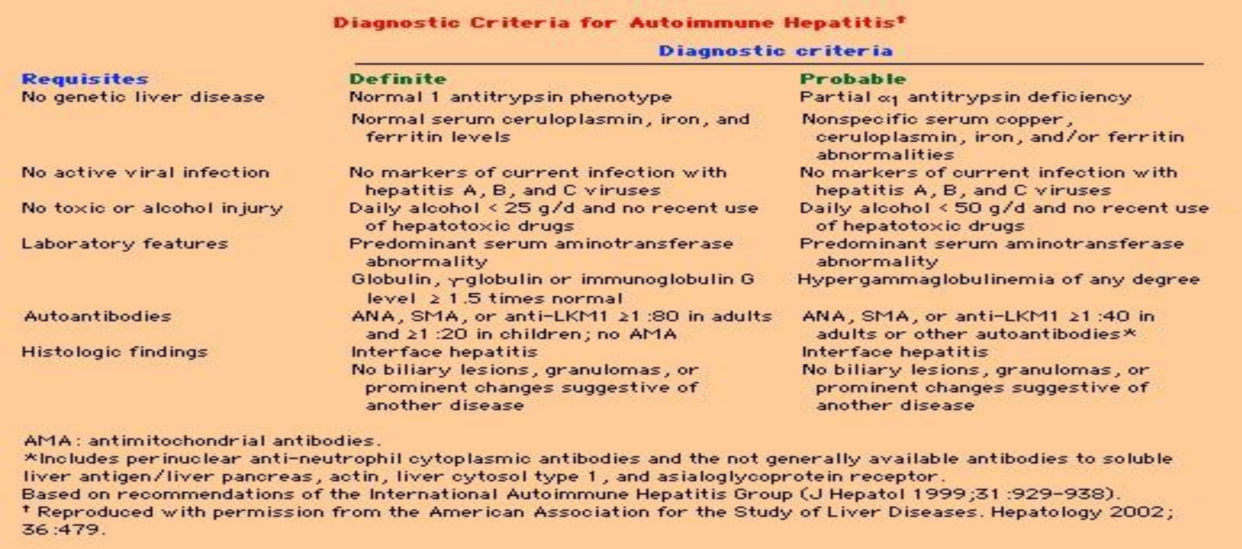
Diagnosis

Diagnostic Criteria

- Exclusion of other causes of liver disease (genetic disorders, viral hepatitis, drug hepatotoxicity, & alcohol).
- Marked hyperglobulinemia and high-titer circulating ANA and other autoantibodies;
- *Characteristic histologic features (interface hepatitis, plasma cells, rosettes)*

Factors that weigh in favor of the diagnosis include:

- *Female gender*
- Predominant aminotransferase elevation → >10 times normal in severe cases
- concurrent other autoimmune diseases → Occasionally arthritis, maculopapular eruptions (including cutaneous vasculitis), erythema nodosum, colitis, pleurisy, pericarditis, anemia, azotemia, and sicca syndrome (keratoconjunctivitis, xerostomia) occur.
- Many patients with autoimmune hepatitis have **normal serum bilirubin**, **alkaline phosphatase**, and **globulin levels** with only **minimal aminotransferase elevations**.
- In severe cases, the serum **bilirubin level is moderately elevated (3 - 10 mg/dL).**



Diagnostic Criteria for Autoimmune Hepatitis[†]

	Diagnostic criteria	
Requisites	**Definite**	**Probable**
No genetic liver disease	Normal 1 antitrypsin phenotype	Partial α_1 antitrypsin deficiency
	Normal serum ceruloplasmin, iron, and ferritin levels	Nonspecific serum copper, ceruloplasmin, iron, and/or ferritin abnormalities
No active viral infection	No markers of current infection with hepatitis A, B, and C viruses	No markers of current infection with hepatitis A, B, and C viruses
No toxic or alcohol injury	Daily alcohol < 25 g/d and no recent use of hepatotoxic drugs	Daily alcohol < 50 g/d and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality	Predominant serum aminotransferase abnormality
	Globulin, γ-globulin or immunoglobulin G level ≥ 1.5 times normal	Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM1 ≥1:80 in adults and ≥1:20 in children; no AMA	ANA, SMA, or anti-LKM1 ≥1:40 in adults or other autoantibodies*
Histologic findings	Interface hepatitis	Interface hepatitis
	No biliary lesions, granulomas, or prominent changes suggestive of another disease	No biliary lesions, granulomas, or prominent changes suggestive of another disease

AMA: antimitochondrial antibodies.

*Includes perinuclear anti-neutrophil cytoplasmic antibodies and the not generally available antibodies to soluble liver antigen/liver pancreas, actin, liver cytosol type 1, and asialoglycoprotein receptor.

Based on recommendations of the International Autoimmune Hepatitis Group (J Hepatol 1999;31:929-938).

[†] Reproduced with permission from the American Association for the Study of Liver Diseases. Hepatology 2002; 36:479.

Management

- Treatment Should be based on: *Severity of symptoms*, *Degree of elevation in transaminases and IgG*, *Histologic findings*, *Potential side effects of treatment*.
- Unfortunately, therapy has not been shown to prevent ultimate progression to cirrhosis
- AASLD Recommendations
  - Treat if serum aminotransferases are > 10 times normal
  - Treat if serum aminotransferases are > 5 times normal and IgG is elevated to > 2 times normal
  - In patients with inactive cirrhosis → evaluate for preexisting comorbidities (hep C), pregnancy, and drug intolerances (increased risk of steroid side effects in pts with DM, osteoporosis, HTN)
  - The mainstay of management in autoimmune hepatitis is **glucocorticoid therapy.**
    - ✓ Prednisone 60mg PO daily with a taper down to 30mg at the 4th week into treatment and then maintenance of 20mg daily until reach endpoint
    - ✓ Reasons for Prednisone only: *Cytopenia, TPMT deficiency, Malignancy, Pregnancy*

  COMBINATION THERAPY
    - ✓ **Prednisone:** start at 30mg daily and taper down to 15mg at week 4, then maintain on 10mg daily until therapy endpoint PLUS
    - ✓ **Azathioprine** 50mg daily
  - The **advantage of the combination** approach is a **reduction** *Over the span of an 18-month course of therapy in serious,* ***life-threatening complications of steroid therapy*** *from 66% down to under 20%*
  - **6-mercaptopurine** may be substituted for its prodrug azathioprine, but this is rarely required

  - Azathioprine alone, however, is not effective in achieving remission, nor is alternative for glucocorticoid therapy.

TREATMENT REMISSION

- Disappearance of symptoms
- Normal serum bilirubin and IgG
- Serum aminotransferases normal or less than twice normal
- Normal hepatic tissue or minimal inflammation and no interface hepatitis.
- Action: **d/c azathioprine and taper prednisone**

TREATMENT FAILURE

- Worsening clinical, laboratory and histologic findins despite compliance with therapy
- Increase in aminotransferases by >60%
- Action: **increase prednisone to 60mg daily and azathioprine to 150mg daily for one month**
- Treatment failures are frequent in patients with established cirrhosis, HLA-DR3 or in patients who present with disease at a younger age and with a longer duration of symptoms

INCOMPLETE RESPONSE

- Some or no improvement in clinical, laboratory or histologic feature
- Failure to achieve remission after 3 years
- Action: **indefinite treatment**

LIVER TRANSPLANTATION

- Patients with **ascites and hepatic encephalopathy** → consider liver transplant if they have failed glucocorticoid therapy.
- Considered in patients with **multi lobar necrosis and have at least one laboratory parameter which does not normalize within 2 weeks** of treatment (these patients have a high immediate mortality rate).
- Considered in pts who **worsen while on glucocorticoid therapy**.

Prognosis

- If untreated approximately 40% die within 6 months, 40% will develop cirrhosis
- *the natural history of milder disease is variable, often accentuated by spontaneous remissions and exacerbations. In treated autoimmune hepatitis, the 10-year survival is 80 - 90%.*
- 13-20% of patients can have spontaneous resolution.
- Poor prognostic signs include:
  - *The presence histologically of multi lobular collapse at the time of initial presentation*
  - **ascites and hepatic encephalopathy**
  - *Failure of the bilirubin to improve after 2 weeks of therapy*
- Death may result from hepatic failure, hepatic coma, other complications of cirrhosis (e.g., variceal hemorrhage), and intercurrent infection.

- In patients with established cirrhosis, HCC may be a late complication but occurs less frequently than in cirrhosis associated with viral hepatitis.

9.2.4 Genetic, metabolic and infiltrative diseases affecting the liver

- **Inherited disorders** include **hemochromatosis, Wilson's disease, α_1 antitrypsin (α_1AT) deficiency, and cystic fibrosis (CF).**
    - Hemochromatosis is the most common inherited disorder affecting Caucasian populations
    - **A hint for diagnosis of genetic disorders may be existent of disease at a relatively young age or a family history of liver disease.**
- From **metabolic disorders**, nonalcoholic fatty liver disease (**NAFLD**) is the most common cause of elevated liver enzymes. *nonalcoholic steatohepatitis (**NASH**) is relatively rare*
- **Infiltrative disorders** of the liver are relatively rare → **Lipid storage diseases (Gaucher's and Niemann-Pick disease), Amyloidosis, sarcoidosis, etc**

9.2.4.1 Hereditary Hemochromatosis

- Hemochromatosis is Iron in Hepatocytes.
- Hemochromatosis can be
- **Primary or Hereditary hemochromatosis;** Common in young age and usually have positive family history, in addition to liver it can also affect heart, pancreas (Causing DM which is more common than DM from Wilsons disease), skin, GI malignancy (e.g. HCC)
- **Secondary hemochromatosis;** secondary to hemolytic anemia, dietary Iron overload, blood transfusion etc.
- Hereditary hemochromatosis (HH) is a common inherited disorder of iron metabolism.
- Most patients with HH are asymptomatic; however, when patients present with symptoms, they are frequently nonspecific and include weakness, fatigue, lethargy, and weight loss.
- Specific, organ-related symptoms include abdominal pain, arthralgias, and symptoms and signs of chronic liver disease.
- Look at IX section of CLD for serum ferritin interpretation

Treatment

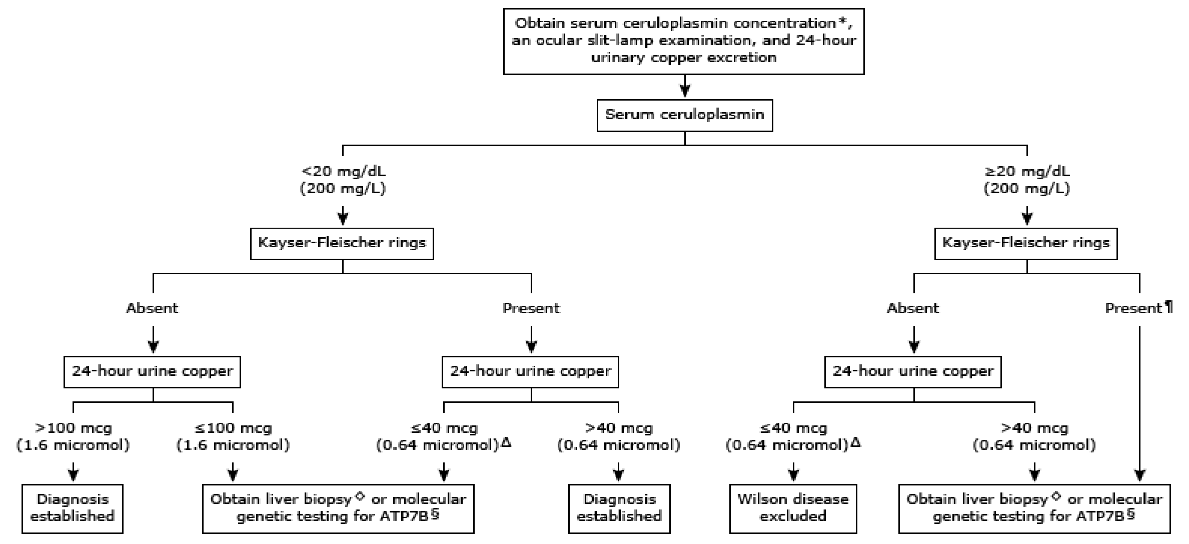
- **weekly phlebotomy** aimed to reduce iron stores, recognizing that each unit of blood contains 200 to 250 mg of iron.
- **Maintenance phlebotomy** is required in most patients and usually can be achieved with **1 unit of blood removed every 2 - 3 months**

9.2.4.2 Wilson's disease

- **Wilson's disease is an inherited disorder of copper homeostasis.** in patients with mutations in *ATP7B*, copper is retained in the liver, leading to increased copper storage & ultimately liver disease as a result
- The clinical presentation of Wilson's disease is variable and includes chronic hepatitis, hepatic steatosis, and cirrhosis in adolescents and young adults
- **Wilson's disease is a multisystem disease with predilection to liver**. It can also involve Brain (various speech and movement disorders), Pancreas (DM), eyes (Kayser-Fleischer rings), heart (rCMP), and hematologic disorders.
- **Neurologic manifestations** indicate that liver disease is present and include various speech and movement disorders **(Dysarthria, Dystonia, Tremor, Parkinsonism, Choreoathetosis, Cerebellar ataxia, Cognitive impairment…)**.
- **Diagnosis** includes the demonstration of:

  A reduced ceruloplasmin level
  An elevated hepatic copper level
  Increased urinary excretion of copper and
  The presence of ***Kayser-Fleischer rings*** *in the corneas of the eyes*

Approach to the diagnosis of Wilson disease


Obtain serum ceruloplasmin concentration*, an ocular slit-lamp examination, and 24-hour urinary copper excretion
Serum ceruloplasmin
<20 mg/dL (200 mg/L)
≥20 mg/dL (200 mg/L)
Kayser-Fleischer rings
Kayser-Fleischer rings
Absent
Present
Absent
Present¶
24-hour urine copper
24-hour urine copper
24-hour urine copper
>100 mcg (1.6 micromol)
≤100 mcg (1.6 micromol)
≤40 mcg (0.64 micromol)Δ
>40 mcg (0.64 micromol)
≤40 mcg (0.64 micromol)Δ
>40 mcg (0.64 micromol)
Diagnosis established
Obtain liver biopsy◊ or molecular genetic testing for ATP7B§
Diagnosis established
Wilson disease excluded
Obtain liver biopsy◊ or molecular genetic testing for ATP7B§

Treatment

Treatment consists of **copper-chelating medications** such as **D-penicillamine and trientine.**

A role for **zinc acetate** has also been established.

Medical treatment is lifelong, and severe relapses leading to liver failure and death can occur with cessation of therapy.

Liver transplantation is curative with respect to the underlying metabolic defect and restores the normal phenotype with respect to copper homeostasis.

9.2.4.3 AAT (α_1 ANTITRYPSIN) deficiency

- AAT is a glycoprotein produced in hepatocytes, phagocytes, and epithelial cells in the lungs, which inhibits serine proteases, primarily neutrophil elastase.
- In AAT deficiency, increased amounts of neutrophil elastase can result in progressive lung injury from degradation of elastin leading to **premature emphysema.**
- **AAT deficiency is known to be a cause of liver disease in infancy, early childhood, adolescence, and in adults.**
- The natural history of AAT deficiency is quite variable. Because of genetic variation, many individuals never develop disease, whereas others can develop childhood cirrhosis leading to liver transplantation.
- A hint to diagnosis may be coexistent lung disease at a relatively young age or a family history of liver and/or lung disease.
- Liver disease may be asymptomatic other than fatigue, or patients may present with complications of decompensated liver disease.
- Diagnosis of AAT deficiency is confirmed by blood tests showing reduced levels of serum AAT
- Liver biopsy is often performed to determine stage of hepatic fibrosis and shows characteristic PAS-positive, diastase-resistant globules in the periphery of the hepatic lobule.

Treatment

- Treatment of AAT deficiency is **usually nonspecific and supportive.**
- For patients with liver involvement, other sources of liver injury, such as **alcohol, should be avoided.**
- Evidence for **other liver diseases** (e.g., viral hepatitis B and C
- hemochromatosis, NAFLD, etc.) **should be sought and treated if possible.**
- **Smoking** can worsen lung disease progression in AAT and **should be discontinued.**
- **Patients with lung disease** may be eligible to receive **infusions of AT**, which has been shown to halt further damage to the lungs.
- **If liver disease becomes decompensated, transplantation** should be pursued and is **curative.**
- Finally, risk of HCC is significantly increased in patients with cirrhosis due to AAT deficiency.

9.2.4.4 Nonalcoholic Fatty Liver Diseases(NAFLD) and Nonalcoholic Steatohepatitis(NASH)

- Nonalcoholic fatty liver disease (NAFLD) is the most common CLD in many parts of the world, including the United States (25%). *This data is from the westerns. but in our set up, even though there is no national data, NAFLD and NASH are rare to consider*
- NAFLD is strongly associated with overweight/obesity and insulin resistance.

- However, it can also occur in lean individuals and is particularly common in those with a paucity of adipose depots (i.e., lipodystrophy).
- Risk factors for NAFLD include; increased BMI (50—90% of NAFLD patients are obese), insulin resistance/type II DM, and other parameters indicative of the metabolic syndrome (e.g., systemic hypertension, dyslipidemia, hyperuricemia/gout, cardiovascular disease) in the patient or family members.
- On the other way, NAFLD is an independent risk factor for metabolic syndrome. Patients with NASH are at 2-3 fold increased risk for the development of metabolic syndrome.
- Ethnic/racial factors also appear to influence liver fat accumulation
- **NAFLD encompasses a spectrum of liver pathology with different clinical prognoses.**
- The simple accumulation of triglyceride within hepatocytes (hepatic steatosis) is on the most clinically benign extreme of the spectrum. On the opposite, most clinically ominous extreme, are cirrhosis and primary liver cancer.
- The risk of developing cirrhosis is extremely low in individuals with chronic hepatic steatosis, but increases as steatosis becomes complicated by histologically conspicuous hepatocyte death and inflammation (i.e., nonalcoholic steatohepatitis [NASH]).
- **NASH literally means fat in hepatocytes and it is histologic definition form of NAFLD.**
- NASH itself is also a heterogeneous condition; sometimes it improves to steatosis or normal histology, sometimes it remains relatively stable for years, but sometimes it results in progressive accumulation of fibrous scar that eventuates in cirrhosis.
- **Many patients can have advanced fibrosis with NASH and even cirrhosis due to NASH with normal liver enzymes**
- Once NAFLD-related cirrhosis develops, the annual incidence of primary liver cancer can be as high as 3%.
- NASH is present in about 25% of individuals who have NAFLD
- The mechanisms underlying the pathogenesis and progression of NAFLD are not entirely clear.
- Hepatic steatosis is proven to result when hepatocyte mechanisms for triglyceride synthesis (e.g., lipid uptake and de novo lipogenesis) overwhelm mechanisms for triglyceride disposal (e.g., degradative metabolism and lipoprotein export), leading to accumulation of fat (i.e., triglyceride) within hepatocytes. So, the net result is hepatic triglyceride accumulation (i.e., steatosis). Obesity and Insulin resistance are the most important risk factors for NASH pathogenesis.
- Triglyceride per se is not hepatotoxic. However, its precursors (e.g., fatty acids and diacylglycerols) and metabolic by-products (e.g., reactive oxygen species) may damage hepatocytes, leading to hepatocyte death and lipotoxicity.
- NASH is the morphologic manifestation of lipotoxicity and resultant wound healing responses
- **Cirrhosis and liver cancer are potential outcomes of chronic NASH.**

DIAGNOSIS

- The diagnosis of NAFLD and NASH is **clinical.**
- Diagnosing NAFLD requires demonstration of increased liver fat in the absence of hazardous levels of alcohol consumption ***(<20 g/d of alcohol be consumed to exclude alcoholic liver disease).***
- **hazardous levels of alcohol consumption defined as > 1 drink per day in women or > 2 drinks per day in men** based on epidemiologic evidence that the prevalence of serum aminotransferase elevations increases when alcohol consumption habitually exceeds these levels.
- One drink is defined as having 10 g of ethanol and, thus, is equivalent to one can of beer, 4 ounces of wine, or 1.5 ounces (one shot) of distilled spirits.
- **It is a diagnosis of exclusion.** Other causes of liver fat accumulation (particularly exposure to certain drugs) and liver injury (e.g., viral hepatitis, autoimmune liver disease, iron or copper overload, α1 antitrypsin deficiency) must also be excluded.
- **Confidence in the diagnosis of NAFLD is increased by identification of NAFLD risk factors.**
- There is yet **no one specific blood test for NAFLD**
- **Abdominal Ultrasound;** is an acceptable first-line test; **CT or MRI** enhances sensitivity for liver fat detection but adds expense.
- It is important to emphasize that the liver may not be enlarged, **Lever enzymes and LFT** (e.g., bilirubin, albumin, prothrombin time) **may be completely normal, in individuals with NAFLD**
- In **Liver biopsy**, the histologic features of NASH are very similar to those seen in alcoholic liver disease; **Mallory's hyaline** can be seen in both disorders, although the number of hepatocytes containing Mallory's hyaline and the size of the deposits are frequently greater in alcoholic liver disease than in NASH.

TREATMENT

- Treatment of NAFLD can be divided into **three components:**
  - **Specific therapy of NAFLD-related liver disease**
  - **Treatment of NAFLD associated comorbidities**
  - **Treatment of the complications of advanced NAFLD** → Which involves management of the complications of cirrhosis and portal hypertension, including primary liver cancers.
- **At present, there are no approved therapies for the treatment of NAFLD**. Thus, **the current approach to NAFLD management focuses on treatment to improve the risk factors for NASH ((i.e., obesity, insulin resistance, metabolic syndrome, dyslipidemia)**
- **Lifestyle changes and dietary modification are the foundation for NAFLD treatment.**
- Only patients with NASH or those with features of hepatic fibrosis on liver biopsy are considered currently for targeted pharmacologic therapies.
- **No agent has yet been approved by the FDA for the treatment of NAFLD.** Hence, this remains an area of active research.

9.2.4.5 Other causes of CLD

Primary biliary cirrhosis

- May be asymptomatic or complain of fatigue, pruritus, and non-jaundice skin hyperpigmentation with hepatomegaly.
- There is **prominent alkaline phosphatase elevation** as well as elevations in cholesterol and bilirubin.
- Gold standard diagnosis is antimitochondrial antibodies with liver biopsy as confirmation if showing florid bile duct lesions.
- It is more common in women.

Primary sclerosing cholangitis (PSC)

- PSC is a progressive cholestatic disorder presenting with pruritus, steatorrhea, fat soluble vitamin deficiencies, and metabolic bone disease.
- There is a strong association with IBD, especially ulcerative colitis.
- Diagnosis is best with contrast cholangiography showing diffuse, multifocal strictures and focal dilation of bile ducts, leading to a beaded appearance.
- Non-specific serum immunoglobulins may also be elevated.

9.3 Jaundice and hyper bilirubinemia

- Jaundice, or icterus, is a yellowish discoloration of tissue resulting from the deposition of bilirubin.
- Hyperbilirubinemia is chemical definition for increased serum bilirubin levels
- Tissue deposition of bilirubin occurs only in the presence of **serum hyperbilirubinemia** and is a sign of either **liver disease** or, less often, a **hemolytic disorder**.
- Increased serum bilirubin levels occur when an imbalance exists between bilirubin production and clearance.
- **The presence of scleral icterus indicates a serum bilirubin of at least 3 mg/dL.**
- As serum bilirubin levels rise, **the skin will eventually become yellow in light-skinned patients and even green if the process is long-standing**. The green color is produced by oxidation of bilirubin to biliverdin.
- Another sensitive indicator of increased serum bilirubin is **darkening of the urine (tea- or cola-colored), which is due to the renal excretion of conjugated bilirubin**.
  - **Bilirubinuria indicates an elevation of the direct serum bilirubin** fraction and, therefore, the presence of liver disease

Production and Metabolism of Bilirubin

- Bilirubin is the end product of heme degradation
- The formation of bilirubin occurs in reticuloendothelial cells, primarily in the spleen and liver.
- Hemoglobin (breakdown in RBC) → heme (catalyzed by **heme oxygenase**) → **biliverdin +** carbon monoxide + iron **(biliverdin** catalyzed by **biliverdin reductase)** **→ bilirubin**
- **Bilirubin is virtually insoluble in water. To be transported in blood, bilirubin must be solubilized by its reversible, noncovalent binding to albumin**
- Transfer of bilirubin from blood to bile involves four distinct but interrelated steps
  - 1st; Hepatocellular uptake
  - 2nd; Intracellular binding
  - 3rd; Conjugation
  - 4th; Biliary excretion
- Unconjugated bilirubin bound to albumin is transported to the liver. After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins including proteins in the **glutathione-S-transferase superfamily**
- In the endoplasmic reticulum, bilirubin is solubilized by conjugation to **glucuronic acid**
- Bilirubin is conjugated with one or two glucuronic acid moieties by a specific **uridine diphosphate** (UDP)-glucuronosyltransferase to form bilirubin mono- and diglucuronide, respectively. These glucuronide conjugates are highly soluble in water.
- The now hydrophilic bilirubin conjugates diffuse from the endoplasmic reticulum to the canalicular membrane,
- Conjugation is obligatory for excretion of bilirubin across the bile canalicular membrane into bile. So, the conjugated bilirubin excreted into bile drains into the duodenum and passes unchanged through the proximal small bowel. Conjugated bilirubin is not taken up by the intestinal mucosa.
- When the conjugated bilirubin reaches the distal ileum and colon, It is hydrolyzed to unconjugated bilirubin by **bacterial β-glucuronidases.**
- The unconjugated bilirubin is reduced by normal gut bacteria to form **urobilinogens.**
  - About 80 - 90% of these products are excreted in feces, either unchanged or oxidized to orange derivatives called **urobilins.**
  - The remaining 10 - 20% of the urobilinogens are passively absorbed, enter the portal venous blood, and are reexcreted by the liver.
  - A small fraction (usually <3 mg/dL) escapes hepatic uptake, filters across the renal glomerulus, and is excreted in urine.
- Unconjugated bilirubin is not excreted in urine, as it is too tightly bound to albumin for effective glomerular filtration and there is no tubular mechanism for its renal secretion.
- In contrast, the bilirubin conjugates are readily filtered at the glomerulus and can appear in urine in disorders characterized by increased bilirubin conjugates in the circulation.

- It should be kept in mind that the kidney can serve as an “overflow valve” for conjugated bilirubin.

Measurement of Serum Bilirubin

- **The terms *direct* and *indirect* bilirubin – that is, conjugated and unconjugated bilirubin, respectively** – are based on the original van den Bergh reaction.
- With the van den Bergh method, **the normal serum bilirubin concentration usually is between 1 and 1.5 mg/dL. Total serum bilirubin concentrations are between 0.2 and 0.9 mg/dL in 95% of a normal population**.
- With this method, the direct fraction provides an approximation of the conjugated bilirubin level in serum. The indirect fraction is the difference between the total and the direct bilirubin levels and provides an estimate of the unconjugated bilirubin in serum.
- **Unconjugated (indirect) hyperbilirubinemia is present when the direct fraction is <15% of the total serum bilirubin.**

$$i.e\ \ ratio = \frac{direct\ bilirubin}{Total\ bilirubin}\ x\ 100\ \%$$

$$Ratio\ > 15\%\ implies\ direct\ hyperbiliribinemia$$

$$Ratio\ < \ 15\%\ implies\ indirect\ hyperbiliribinemia$$

- The presence of even limited amounts of true conjugated bilirubin in serum suggests significant hepatobiliary pathology.
- As conjugated hyperbilirubinemia is always associated with bilirubinuria (except in the presence of delta bilirubin in prolonged cholestasis when jaundice is overt), detection of bilirubin in urine via dipstick test is extremely helpful to confirm the presence of conjugated hyperbilirubinemia in a patient with mildly elevated direct fraction.
- Unconjugated bilirubin is always bound to albumin in the serum, is not filtered by the kidney, and is not found in the urine.
- **Any bilirubin found in the urine is conjugated bilirubin.**
- The presence of bilirubinuria on urine dipstick test (Ictotest) indicates an elevation of the conjugated bilirubin fraction that cannot be excreted from the liver, and implies the presence of hepatobiliary disease.

Approach to a Patient with Jaundice

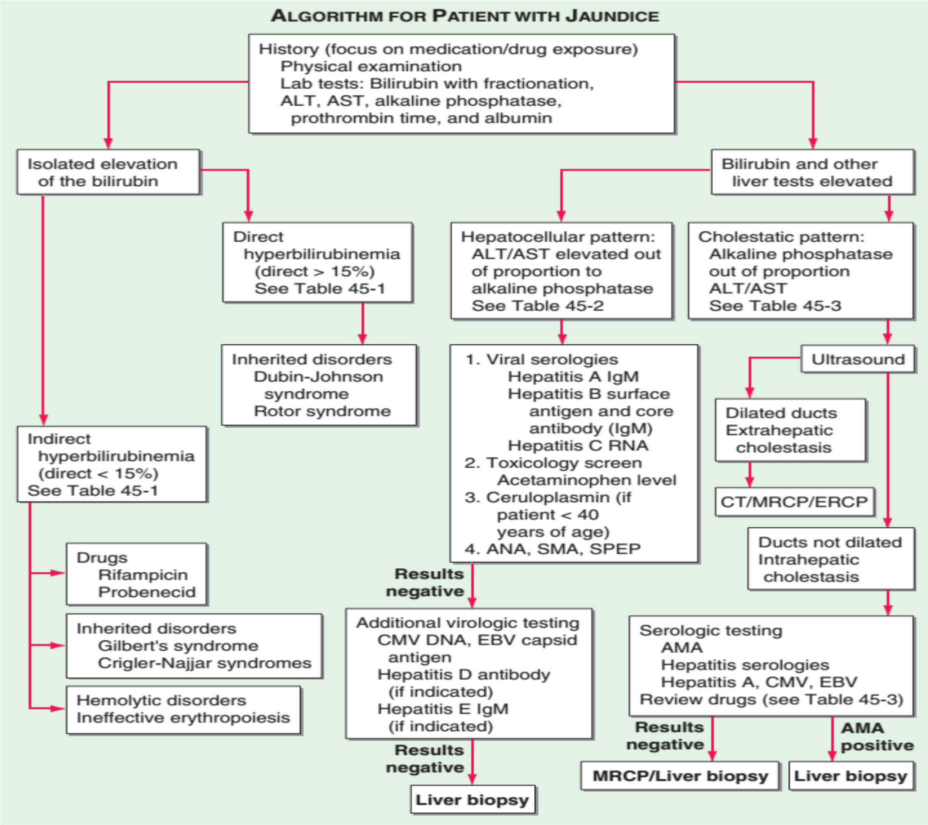

ALGORITHM FOR PATIENT WITH JAUNDICE
History (focus on medication/drug exposure) Physical examination Lab tests: Bilirubin with fractionation, ALT, AST, alkaline phosphatase, prothrombin time, and albumin
Isolated elevation of the bilirubin
Bilirubin and other liver tests elevated
Direct hyperbilirubinemia (direct > 15%) See Table 45-1
Hepatocellular pattern: ALT/AST elevated out of proportion to alkaline phosphatase See Table 45-2
Cholestatic pattern: Alkaline phosphatase out of proportion ALT/AST See Table 45-3
Inherited disorders Dubin-Johnson syndrome Rotor syndrome
1. Viral serologies Hepatitis A IgM Hepatitis B surface antigen and core antibody (IgM) Hepatitis C RNA 2. Toxicology screen Acetaminophen level 3. Ceruloplasmin (if patient < 40 years of age) 4. ANA, SMA, SPEP
Ultrasound
Dilated ducts Extrahepatic cholestasis
CT/MRCP/ERCP
Ducts not dilated Intrahepatic cholestasis
Indirect hyperbilirubinemia (direct < 15%) See Table 45-1
Drugs Rifampicin Probenecid
Inherited disorders Gilbert's syndrome Crigler-Najjar syndromes
Hemolytic disorders Ineffective erythropoiesis
Results negative
Additional virologic testing CMV DNA, EBV capsid antigen Hepatitis D antibody (if indicated) Hepatitis E IgM (if indicated)
Results negative
Liver biopsy
Serologic testing AMA Hepatitis serologies Hepatitis A, CMV, EBV Review drugs (see Table 45-3)
Results negative
AMA positive
MRCP/Liver biopsy
Liver biopsy

FIGURE 45-1 **Evaluation of the patient with jaundice;** ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; LKM, liver-kidney microsomal antibody; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis.

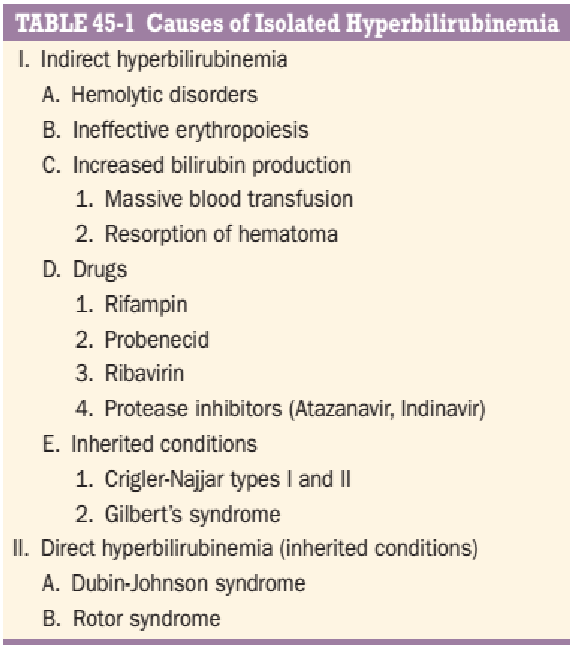


TABLE 45-1 Causes of Isolated Hyperbilirubinemia
I. Indirect hyperbilirubinemia
A. Hemolytic disorders
B. Ineffective erythropoiesis
C. Increased bilirubin production
1. Massive blood transfusion
2. Resorption of hematoma
D. Drugs
1. Rifampin
2. Probenecid
3. Ribavirin
4. Protease inhibitors (Atazanavir, Indinavir)
E. Inherited conditions
1. Crigler-Najjar types I and II
2. Gilbert's syndrome
II. Direct hyperbilirubinemia (inherited conditions)
A. Dubin-Johnson syndrome
B. Rotor syndrome

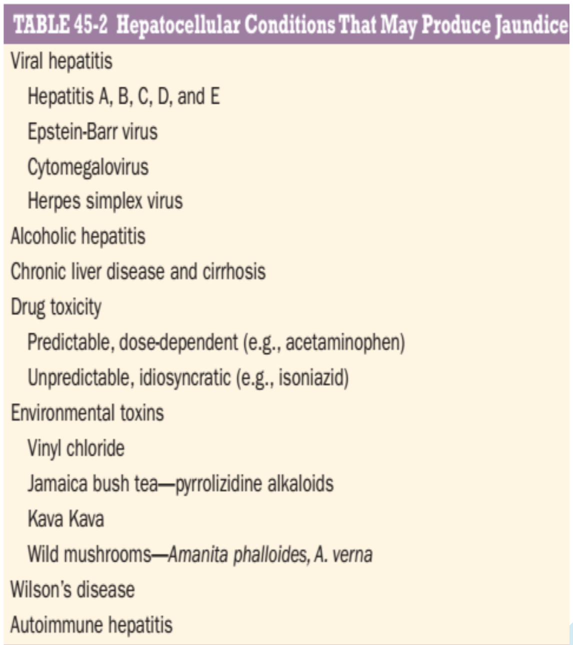


TABLE 45-2 Hepatocellular Conditions That May Produce Jaundice
Viral hepatitis
Hepatitis A, B, C, D, and E
Epstein-Barr virus
Cytomegalovirus
Herpes simplex virus
Alcoholic hepatitis
Chronic liver disease and cirrhosis
Drug toxicity
Predictable, dose-dependent (e.g., acetaminophen)
Unpredictable, idiosyncratic (e.g., isoniazid)
Environmental toxins
Vinyl chloride
Jamaica bush tea—pyrrolizidine alkaloids
Kava Kava
Wild mushrooms—*Amanita phalloides, A. verna*
Wilson's disease
Autoimmune hepatitis

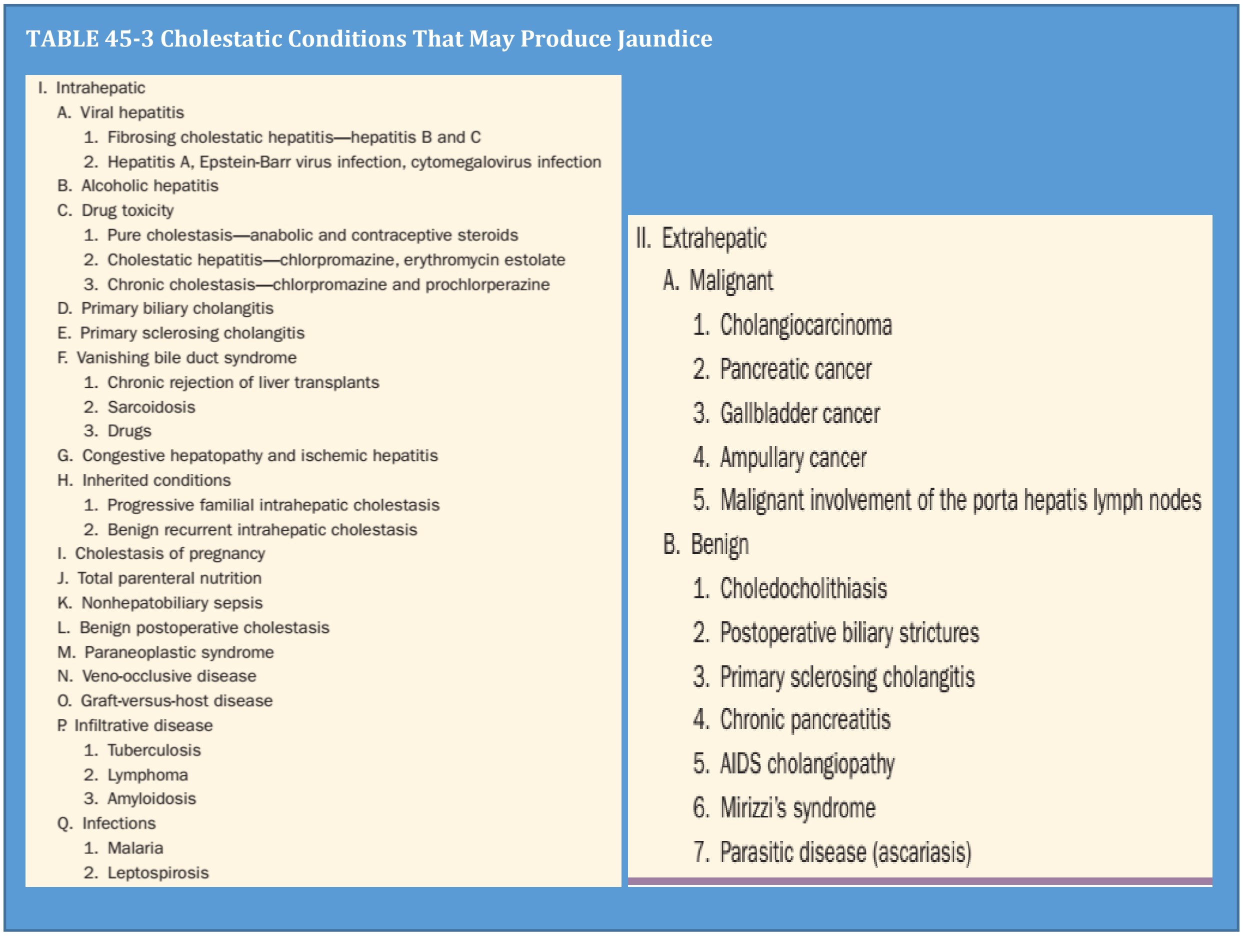


TABLE 45-3 Cholestatic Conditions That May Produce Jaundice

I. Intrahepatic
- A. Viral hepatitis
  - 1. Fibrosing cholestatic hepatitis—hepatitis B and C
  - 2. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection
- B. Alcoholic hepatitis
- C. Drug toxicity
  - 1. Pure cholestasis—anabolic and contraceptive steroids
  - 2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
  - 3. Chronic cholestasis—chlorpromazine and prochlorperazine
- D. Primary biliary cholangitis
- E. Primary sclerosing cholangitis
- F. Vanishing bile duct syndrome
  - 1. Chronic rejection of liver transplants
  - 2. Sarcoidosis
  - 3. Drugs
- G. Congestive hepatopathy and ischemic hepatitis
- H. Inherited conditions
  - 1. Progressive familial intrahepatic cholestasis
  - 2. Benign recurrent intrahepatic cholestasis
- I. Cholestasis of pregnancy
- J. Total parenteral nutrition
- K. Nonhepatobiliary sepsis
- L. Benign postoperative cholestasis
- M. Paraneoplastic syndrome
- N. Veno-occlusive disease
- O. Graft-versus-host disease
- P. Infiltrative disease
  - 1. Tuberculosis
  - 2. Lymphoma
  - 3. Amyloidosis
- Q. Infections
  - 1. Malaria
  - 2. Leptospirosis

II. Extrahepatic
- A. Malignant
  - 1. Cholangiocarcinoma
  - 2. Pancreatic cancer
  - 3. Gallbladder cancer
  - 4. Ampullary cancer
  - 5. Malignant involvement of the porta hepatis lymph nodes
- B. Benign
  - 1. Choledocholithiasis
  - 2. Postoperative biliary strictures
  - 3. Primary sclerosing cholangitis
  - 4. Chronic pancreatitis
  - 5. AIDS cholangiopathy
  - 6. Mirizzi's syndrome
  - 7. Parasitic disease (ascariasis)

Disorders of Bilirubin metabolism leading to unconjugated hyperbilirubinemia

- **Increased Bilirubin production.**
  - **Hemolysis**
  - **Ineffective Erythropoiesis**
  - Degradation of the hemoglobin of extravascular collections of erythrocytes, such as those seen in massive tissue infarctions or large hematomas
- **Decreased Hepatic bilirubin clearance**
  - **Decreased Hepatic Uptake. E.g.** Gilbert's syndrome, Several drugs and cholecystographic contrast agents.
  - **Impaired Conjugation; Physiologic neonatal jaundice, Acquired Conjugation defects**
  - **Hereditary defects in bilirubin conjugation; Crigler-Najjar Syndrome, Type I and type II, Gilbert's Syndrome**

Disorders of Bilirubin metabolism leading to mixed or predominantly conjugated hyperbilirubinemia

- **Almost all are Familial defects in hepatic excretory function which include;**
  - **Dubin-Johnson Syndrome**
  - **Rotor Syndrome**
  - **Benign Recurrent Intrahepatic Cholestasis**
  - **Progressive Familial Intrahepatic Cholestasis**

Chapter 10; DM /Diabetes Mellitus/ (የስኳር በሽታ)

Dr. Mulualem. G

Clinical features and how to write hx of DM patient

History

N.B Type one DM patients usually present with poly symptoms. But type two DM patients may present with complication or Asymptomatic and diagnosed accidentally while patients visit a health facility for other reason.

Poly symptoms (3P)

- **Poly urea** → Write in terms of Day to Night ratio (e.g. poly urea of 8:6 day to night ratio).
    - The 24-hour urine voided by a healthy adult range from 600 to 2000ml
    - **Polyuria considered when there is** consistent elimination of an abnormally large volume of urine, **> 2000ml/24hr**
- **Polydipsia** → ask How much litre of water he/she drinks per day
- **Polyphagia** → less common smx than Polydipsia and Poly urea

- Weight loss despite increased appetite
- Generalized weakness or malaise
- DKA smx's like Vomiting, Abdominal pain and LOC
- Recurrent skin infections
- Recurrent itching of the vulva (candida infections)
- Symptoms related to chronic complications can be present at initial diagnosis in type II diabetic patients
    - Numbness or pain over the lower limbs
    - Visual impairment Or Blurred vision
    - Foot abnormalities (ulcer, ischemia, deformity)
    - Body swelling
- Hyperglycemia features include → 3P, DKA/HHS, blurring of vision, dry mouth and other signs of DHN especially in HHS

Risk factors

For Type II DM*	For Type I DM*
The ADA recommends screening All Individuals >45 years every 3 years and Screening individuals at An Earlier Age if they are Overweight [BMI >25 kg/m^2] and Have One additional Risk Factor for diabetes	✓ Genetic (abnormality in HLA ***region** on Chromosome 6*) ○ *The concordance of type 1 DM in identical twins ranges between*

- **Individuals with any one of the following need screening for type II diabetes. If the result is normal, repeat screening every 3 years; but if the result is in the prediabetes range repeat the test every year.**

- ✓ HTN
- ✓ Dyslipidemia (HDL < 35mg/dl and/or triglyceride level > 250mg/dl)
- ✓ Family history (First-degree relative with diabetes)
    - ○ Type II DM pts have strong genetic association than type I DM
    - ○ *The concordance of type II DM in identical twins is between **70 and 90%.***
    - ○ *If both parents have type II DM, the risk approaches **40%.***
- ✓ Environmental factors
    - ○ Overweight or central obesity (BMI >25kg/m2)
        - ▪ *≥ **80%** of type II DM pt's are Obese*
    - ○ Physical inactivity
    - ○ Increased intake of Raw meat, fat and lipid containing food
    - ○ Smoking
    - ○ Alcohol intake
- ✓ Old age (age ≥ 45)
- ✓ Ethnicity→ common in African American
- ✓ Individuals with prediabetes should be tested yearly
- ✓ PCOS (polycystic ovary sxx) in females or acanthosis nigricans
- ✓ History of atherosclerotic Cardiovascular disease
- ✓ Drugs → steroids (prednisolone), Phenytoin, thiazide
- ✓ Women with history of GDM (gestational DM)
- ✓ Chronic pancreatitis
- ✓ Pheochromocytoma
- ✓ Acromegaly

__40 and 60%,__ indicating that additional modifying factors are likely involved in determining whether diabetes develops.

- ○ *Although the risk of developing type 1 DM is increased **tenfold** in relatives of individuals with the disease, the risk is relatively low: **3—4%** if the **Parent** has type 1 diabetes and **5—15%** in a **Sibling** (depending on which HLA haplotypes are shared). Hence, most individuals with type 1 DM do not have a first-degree relative with this disorder.*
- ✓ Autoimmunity→ like Hashimoto's thyroiditis
- ✓ Environmental factors
    - ○ Diet→cow milk during infancy→ antibody to cow insulin is similar to human insulin known as antigen mimickeracy
    - ○ Toxin → which affect pancreatic B cells
    - ○ Mumps, rubella, coxsackie infection
- ✓ Young age (age <30)

*no clear-cut boundary for Type I & II DM in RF. One can be RF for the other.

N.B Metabolic SXX

- ✓ a.k.a syndrome x, insulin resistance sxx, obesity dyslipidaemia sxx
- ✓ It Includes (Mnemonics → Angeles Have Healthy Life style)
    - ○ Abdominal obesity (BMI > 40 kg/m^2 for male and >30 kg/m^2 for female or waist circumference >102 cm for male and >88 for female)
    - ○ Hyperglycemia (DM)
    - ○ HTN
    - ○ Lipid abnormality (Hyperlipidemia, dyslipidemia)

Complication of DM

1. **Acute complications**
    - **DKA**
    - **HHS**
    - **Hypoglycaemia**
    - Infection
    - Lactic acidosis
  - *Acute complications may occur at any stage of the disease*

Chronic complications

- *Chronic Complications begin to appear during the Second Decade of hyperglycemia.*
- *Individuals with previously undetected Type II DM may present with chronic complications of DM at the time of diagnosis.*
- Classified as microvascular, macrovascular and avascular complications

- **Micro vascular**
    - Retinopathy (Non proliferative or proliferative), Macular oedema
        - *Almost everyone with Type I DM will eventually develop Nonproliferative Retinopathy. But luckily, the retinopathy that destroys vision, Proliferative Retinopathy, is far less common.*
    - Neuropathy
        - It can be Mono neuropathy, poly neuropathy, mono neuropathy multiplex or autonomic neuropathy
        - Most common (50-75%) cause of non-traumatic foot Amputation
    - Nephropathy
        - DM is most common cause of renal insufficiency or renal failure.
        - ESRD is more common in Type I DM than Type II DM
        - Diabetic Nephropathy have 5 stages
            1) Renomegaly, increased GFR
            2) Basement membrane thickening
            3) Micro albuminuria (30-300 mg/dl)
            4) Macro albuminuria (>300 mg/dl)
            5) ESRD (End stage renal disease), Uraemia, HTN
- **Macro vascular**
    - CAD (coronary artery disease like MI & IHD. **N.B DM is the most common cause of Silent MI** (the so called **"DM is silent killer"**))
    - CVA (cerebrovascular Attack like stroke & TIA)
    - PAD (Peripheral arterial disease)
- **Avascular**
    - GIT
        - Gastro paresis → manifest with Diarrhoea, post prandial bloating, fullness and discomfort, intestinal obstruction
        - Motility disorders → atony (manifest with constipation) or hypersonic (manifest with Diabetic Diarrhoea)
    - GUS → uropathy, sexual dysfunction (like decreased libido, impotence)
    - Skin → diabetic foot ulcer (cellulitis, gangrene)

- Infections → UTI, pneumonia, periodontal infection, Malignant Otitis externa (specific to DM), Rhino orbito cerebro mucoro mycosis (extremely rare but specific to DM)
- Cataract, glaucoma
- Bone destruction
- Others which are specific to DM
    - Acalculous cholecystitis
    - Tubular papillary necrosis (ATN)
    - Volvo vaginal candidiasis, oral candidiasis

Look at Screening and management of Chronic complications of DM below under management section

Sample history

Chief compliant

polydipsia and polyuria of three weeks duration

HPI

This patient was last relatively healthy 03 weeks back at which time he started to experience polyuria of 7- 8 times during night and 10-12 times during daytime with increased feeling of thirst for which he drinks 4 - 6 liters of water per day but no polyphagia.

Associated with this he also experienced unquantified but significant weight loss to the extent his trousers become loose despite increased appetite, generalized weakness to the extent he couldn't perform his routine daily activities.

For this complaint he visited a private clinic in Gondar town where he was told to have increased blood sugar level and referred to our hospital for better investigation and management. From the referral paper, RBS was 350mg/dl and repeated on next day of first determination and the value was 289 mg/dl, FBS was 194 mg/dl, from U/A glucose was +2 and ketone free but no treatment given.

- No family hx of similar illness *(Genetics)*
- No self or family hx of HTN *(RF)*
- No hx smoking or chronic alcohol intake *(RF)*
- No hx of Drug *(prednisolone, thiazide, phenytoin predispose to DM, lithium and diuretics are DDX for polyuria)*
- He/she usually eats injera made of "teff" and "machilla" and "wott" made of "atter" and "dagusa" 3-4 times per day. Occasionally he eats meat during holidays *(Increased intake of Raw meat, fat and lipid containing food are RF for DM)*
- No hx of Anterior neck swelling, heat intolerance, profuse sweating, sleep disturbance, palpitation, tremor or irritability *(autoimmune disease like Hashimoto's thyroiditis can occur concomitantly with Type I DM)*
- No hx of LOC, Abdominal pain or Vomiting (DKA→CXN)

- No hx of blurring of vision, eye pain or discharge *(retinopathy →CXN)*
- No hx of Flank pain, dysuria, hematuria, urgency or frequency *(Nephropathy, UTI →CXN)*
- No hx of numbness, tingling, burning sensation, or wound over the body *(DM patients don't sense pain during trauma due to neuropathy which predispose to Diabetic ulcer →CXN)*
- No hx of body weakness or sensory loss *(CVA like stroke →CXN)*
- No hx of chest pain, Dyspnea, orthopnea, PND or Palpitation (CAD/MI/ ending up in CHF →CXN)
- No hx of cough, fever or fast breathing (pneumonia →CXN)
- No hx of intermittent claudication, bluish discoloration of skin, cold skin or skin Ulcer (PAD →CXN)
- No hx Nausea, vomiting, diarrhoea, or constipation *(Gastroparesis, motility disorder →CXN)*
- No hx of Head injury or Neurosurgery (central Diabetic Insidious→ DDX)

Finally, he was admitted to our hospital walking by himself.

Physical examination (pertinent findings)

In your physical examination assess signs of DKA and Diabetic Foot ulcer together with these pertinent findings.

1 GA

- Obesity
- Cushionoid face

Vital signs

- OHT→ due to Autonomic neuropathy
- HTN → >130/80 is HTN in DM
- Resting tachycardia → due to Autonomic neuropathy
- Obesity → calculate BMI and measure Waist circumference

HEENT

- Hair loss
- Periorbital swelling → Mucor mycosis
- Active Ear discharge → Malignant otitis externa
- Oral thrush → oral candidiasis
- Poor dental hygiene (tooth loss)
- Xanthelasma → N.B it is common around eye lids and Achilles tendon
- Cataract

LGS

- Thyroid enlargement → poly glandular autoimmune disorder (PGAID)
- Loss of sweating → due to Autonomic neuropathy

RS

- Signs of consolidation → pneumonia (common infection in DM)

CVS

- ✓ Arterial examination especially posterior tibial artery and dorsalis pedis artery (PAD)
- ✓ IHD

Abdominal examination

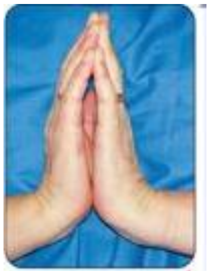
- ✓ Hepatomegaly → from fatty liver
- ✓ Abdominal distention → from Gastroparesis or atony
- ✓ Intestinal obstruction → from autonomic neuropathy
- ✓ Murphy sign +ve → acalculous cholecystitis

GUS

- ✓ Supra pubic tenderness or CVAT → UTI, pyelonephritis
- ✓ Active vaginal discharge or whitish plaque → vaginal candidiasis (common than oral candidiasis)
- ✓ Urinary bladder atony → voiding difficulty → due to Autonomic neuropathy
- ✓ Impotence → due to Autonomic neuropathy

MSS

- ✓ Diabetic foot ulcer
- ✓ Deformities → hammer toes, claw toes, prayers hand sign
- ✓ Duptyrens contracture



Image; prayers sign

IS

- ✓ Cold/dry skin, crackles, fissures → autonomic neuropathy
- ✓ Hair loss
- ✓ Skin atrophy

NS

- ✓ GCS
  - LOC → DKA
- ✓ Cranial nerve
  - Cranial nerve palsy (CN III, IV, VI and VII)
- ✓ Motor
  - Muscle wasting
  - Hypotonia
  - Decreased power
  - Hyporeflexia
  - Peripheral neuropathy
    - Motor neuropathy → foot drop, wrist drop, mono neuropathy multiplex
- ✓ Sensory

- ○ Peripheral neuropathy → distal symmetric polyneuropathy **(DSPN)** which is **glove and stocking** pattern with sensory loss or paraesthesia. Pain and temperature loss are common.

✓ Autonomic neuropathy
- Urinary bladder atony → voiding difficulty
- Impotence
- Resting tachycardia
- Loss of sweating
- GI neuropathy → Gastroparesis, Diabetic diarrhoea

N.B several Rare Infections are seen almost exclusively in the diabetic population. Examples include
- ❖ Rhino-cerebral Mucor-mycosis
- ❖ Emphysematous Infections of the Gall Bladder and Urinary Tract
- ❖ "Malignant" or Invasive Otitis Externa.

DDX

For Patient presenting with polyuria and/or polydipsia

1. DM
2. Diabetic insipidus (DI)

- DI is a disorder resulting from **abnormalities of Antidiuretic hormone (ADH) production from the hypothalamus or ADH action in the kidney.** Final common pathway → no response to ADH
- Characterized by polyuria and polydipsia → the passage of **copious amounts of dilute urine** (**low specific gravity**, usually < **1.010**).
- **There are 4 Types of DI, the 1st two are common forms**

Nephrogenic DI → a.k.a **peripheral DI**. Due to increased resistance of ADH receptors in kidney to ADH

✓ Nephrogenic causes
- Congenital
- Acquired
  - CRF
  - Lithium
  - Hypokalemia
  - Hypercalcemia

Neuropathic DI → a.k.a **central,** hypothalamic, pituitary or neurohypophyseal DI. Caused by decreased secretion or lack of secretion of ADH from posterior pituitary. Head injury or neurosurgery are risk factors for central DI.

- ▪ Central/Cranial causes
  - ➢ Congenital
  - ➢ Acquired

- Post traumatic
- Iatrogenic (post-surgical)
- Tumours
- Infection
- Idiopathic

Gestational DI → Caused by a deficiency of the antidiuretic hormone, vasopressin, that occurs only during pregnancy

Dipsogenic DI → a form of primary polydipsia. Caused by Abnormal thirst and Excessive intake of water or other liquids

3. Drugs → lithium, diuretics (Furosemide, thiazide), Alcohol
4. Pheochromocytoma
5. AKI/CKD
6. Psychogenic polydipsia → patient drinks as he/she assume of being dry mouth, common in mental disorders
7. Hypercalcemia/hypokalaemia
8. Addison's disease
9. ? Cushing sxx

IX

1. Blood sugar → *look at table below under discussion part for ADA diagnostic criteria of DM*
   - ✓ RBS
   - ✓ FBS
   - ✓ OGTT
   - ✓ HbA1c → tells about the past 3 months sugar level. Normal value is 4 - 5.6% of body Haemoglobin.

N.B FBS and HbA1c are reliable for screening

2. U/A → what do you expect from U/A
   - ✓ Glucosuria (glucose +2, +3…)
   - ✓ Ketonuria from DKA (ketone +2, +3…)
   - ✓ Albuminuria from DM nephropathy
   - ✓ WBC casts → suggest infection like UTI, pneumonia, sepsis
3. CBC → what do you expect from CBC
   - ✓ Leukocytosis
   - ✓ Anemia
   - ✓ Ketone bodies
4. Serum electrolyte → hyperkalaemia despite decreased K^+ level in cells because acidosis impairs H^+/ K^+ pump (i.e. impair K^+ absorption from blood stream). K^+ Increase in blood during analysis but hypokalaemia in cells.
5. RFT
6. Lipid profile → increased LDL, Triglyceride, and cholesterol but decreased HDL
7. PICT
8. ECG & CXR → if indicated
9. Serum insulin level and C-peptide → C-peptide < 0.6 ng/dl in Type I DM and > 1 ng/dl in >1-2 years for type II DM (*Serum insulin or C-peptide*

measurements do not always distinguish type 1 from type 2 DM, but a low C-peptide level confirms a patient's need for insulin.

10. Islet cell auto antibody → Anti - GAD (Glutamic acid decarboxylase) & Anti - insulin antibody
11. Blood and urine culture
12. Serum PH and ketone
13. ABG (Arterial blood gas) analysis
    - ✓ PH → acidosis
    - ✓ Serum bicarbonate → low which shows metabolic acidosis
    - ✓ Anion gap = $2Na^+ - (Cl^- + HCO_3^-)$ or $(Na^+ + K^+) - (Cl^- + HCO_3^-)$
    - ✓ O_2 & CO_2 → low CO_2 due to respiratory compensation.

In newly diagnosed patients

- Diagnostic tests: Fasting or random blood glucose, glycated hemoglobin (HbA1c)
- Urine ketones
- Urine albumin
- BUN and creatinine
- Fasting lipid profile
- ECG (adults)

In diagnosed patients, follow up investigations

- Glycemic control: HbA1c, FBS together with post prandial plasma glucose (i.e. RBS 2hr after breakfast, 2hr after lunch, and 2hr after dinner)
- Screening for complications: Urine albumin/protein, retinal screening by ophthalmologist, serum creatinine and urea.
- Other cardiovascular risk screening: Lipid profile (if not already on statin).

Discussion

- **Diabetes Mellitus** (DM) was derived from two words; **Diabetes = "siphon" or "running through"** meaning Large urine volume and **Mellitus = sweet** to indicate Glucose in urine.
- **DM** refers to a heterogenous group of common metabolic disorders that share the phenotype of **hyperglycemia.**
- Several distinct types of DM are caused by a complex interaction of **genetics and environmental factors.**
- Depending on the etiology of the DM, factors contributing to hyperglycemia include **Reduced Insulin Secretion, Decreased Glucose Utilization, and Increased Glucose Production.**
- Diabetes is the leading cause of cardiovascular disease, CKD (**ESRD)**, visual loss and non-traumatic amputations worldwide.

Etiologic classification of diabetes mellitus

The classification of diabetes includes four clinical classes

A. **Type I diabetes** → results from beta cell destruction, leading to **absolute insulin deficiency (complete or near-total insulin deficiency).**

1. **Immune-mediated**
2. **Idiopathic**

B. **Type II diabetes**

- It is a heterogeneous group of disorders characterized by variable degrees of **insulin resistance, impaired insulin secretion**, and **increased glucose production.**
- May range from **predominantly insulin resistance with relative insulin deficiency** to **a predominantly insulin secretary defect with insulin resistance**

C. **Gestational diabetes mellitus (GDM) →** diabetes diagnosed during pregnancy in previously non-diabetic woman

D. **Other specific types of diabetes**

- **Chromosomal abnormalities** (from **MODY 1 to MODY 6**, MODY = Maturity onset diabetes of the young /in youth/)
  - **MODY** is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia (Usually <25 years), and impairment in insulin secretion
- **Genetic defects in insulin action**
- **Diseases of the exocrine pancreas** (Pancreatitis, Trauma/pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis….)
- **Endocrinopathies** (Hyperthyroidism, Acromegaly, Cushing's syndrome,Glucagonoma, Somatostatinoma, Pheochromocytoma, Aldosteronoma…)
- **Drug or chemical induced** (Glucocorticoids, Thyroid hormone, Thiazides, Pentamidine, Nicotinic acid, Beta-adrenergic agonists, Alpha interferon…)
- **Infections** (Congenital rubella, CMV…)
- **Other genetic syndromes** sometimes associated with diabetes (Down syndrome, Klinefelter syndrome, Turner syndrome, Porphyria, Friederich's ataxia….)
- **MRDM (Malnutrition related DM)**
- **Others**

- The clinical course and treatment of the different types of diabetes are different; hence, classification of the type of diabetes is very important to determine therapy.
- The traditional thinking that type II diabetes as the disease of adults and type I diabetes as the disease of children is not accurate as both diseases can occur in both age groups. So, age is not a criterion in the classification system.

- The terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) from previous classifications are obsolete nowadays.
- Since many individuals with type II DM eventually require insulin treatment for control of glycemia, the use of the term NIDDM generated considerable confusion.

Suggestive clues to Differentiate Type I DM from Type II DM*

Type I DM	Type II DM
Common in young age (usually < 30) Normal BMI or lean body mass Usually No immediate family hx Short duration of symptoms (days to weeks) and present with poly symptoms Can present with DKA Management is based on Insulin only GDM is rare in Type I DM Associated with other auto immune disease (like hashimoto's thyroiditis, autoimmune hemolytic anemia, pernicious anemia, coeliac disease, vitiligo) destruction of the pancreatic beta cells and insulin deficiency.	Common in middle aged and elderly > 80 % of pts are obese, but elderly may be lean Usually have +ve family hx Asymptomatic or present with complication (skin infections, pruritis, vulvovaginitis, vascular and avascular cxn) and Symptoms may persist for months or years (i.e. chronic cxn are cmn) Can present with HHS Oral hypoglycemic drugs are mainstay of treatment (unless insulin indicated) GDM is common in Type II DM Associated with metabolic syndrome (DM, HTN, Dyslipidemia, Abdominal obesity) Impaired Insulin Secretion and Insulin Resistance are central to the development of Type II DM.

*no clear-cut boundary for Type I & II DM clinically.

Table. Current ADA diagnostic criteria for diabetes mellitus

Diagnostic test	Normal	Pre-diabetes🕮	Diabetes	Remarks
Fasting blood glucose (FBS)♥	**75 to < 100 mg/dL**	100-125mg/dl	≥126 mg/dl	At least 2 tests needed*
Hemoglobin A1C (HbA1C) #	**4.0 – 5.6%**	5.7-6.4%	≥ 6.5%	At least 2 tests needed*
02-hour plasma glucose tolerance test (OGTT)💣	< 140 mg/dl	140-199mg/dl	≥200mg/dl	At least 2 tests needed
Random blood glucose (RBS)	**65 to < 140 mg/dL**	? 140-199mg/dl	≥200mg/dl	DM diagnosed Only if RBS ≥200mg/dl is accompanied by Classic Symptoms of DM

				(Polyuria, Polydipsia, Weight Loss)

1 mmol/l = 18 mg/dl (e.g ≥126 mg/dl means > 7.0 mmol/l)

* If both fasting blood sugar and hemoglobin A1C are done initially and both are in the diabetic range, repeat test is not necessary for the diagnosis.

# If there is significant discrepancy between HbA1C and blood glucose measurements, use the blood glucose level.

♥ Fasting is defined as no caloric intake for at least 8 hours

☞ OGTT test should be performed (as described by the WHO), using a glucose load containing the equivalent of 75-gram anhydrous glucose dissolved in water. Then measure glucose level after 2 hrs of taking 75-gram glucose (in our set up we use 9 vials of D40, since 1vial of D40 is 8gram, which means 8 x 9 = 72gram)

🕮 Some use the term "increased risk for diabetes" (ADA) or "intermediate hyperglycemia" (WHO) rather than "prediabetes."

🕮 Prediabetes patients are at **Greater Risk** of progressing to **Type II Diabetes** and have an increased risk of **Cardiovascular Disease.**

Insulin secretion and action

- **Glucose** is the key regulator of **insulin secretion by the pancreatic beta cell**, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion.
- **Insulin** is the most important regulator of this Metabolic Equilibrium, but neural input, metabolic signals, and other hormones (e.g., glucagon) result in integrated control of glucose supply and utilization

In the Fasting State

- **low insulin** levels Increase Glucose Production by Promoting Hepatic Gluconeogenesis and Glycogenolysis and Reduce Glucose Uptake In Insulin-Sensitive Tissues (Skeletal Muscle and Fat), Thereby promoting mobilization of Stored Precursors such as Amino Acids and Free Fatty Acids (Lipolysis).
- **Glucagon**, **secreted by Pancreatic Alpha Cells** when blood glucose or insulin levels are low, Stimulates Glycogenolysis and Gluconeogenesis by the Liver and Renal Medulla.

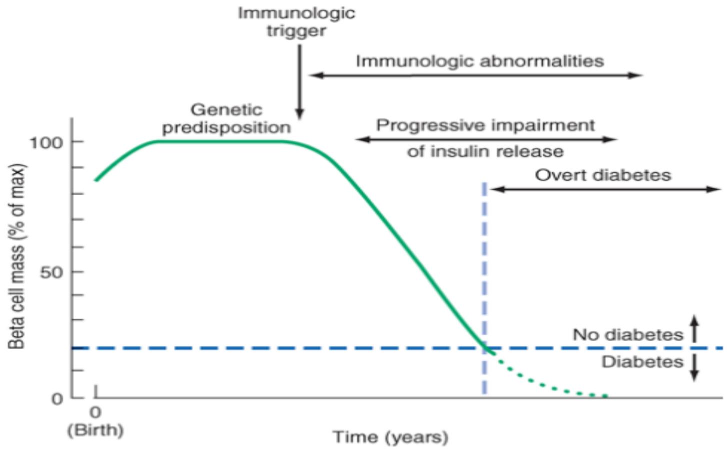
Postprandially

- the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes.
- **Insulin**, An Anabolic Hormone, Promotes the Storage of Carbohydrate and Fat and Protein Synthesis.
- The major portion of Postprandial Glucose is utilized by Skeletal Muscle, an effect of insulin-stimulated glucose uptake.
- Other tissues, most notably the **Brain**, utilize glucose in an insulin-independent fashion.

Pathophysiology

Type I DM

- **Type 1 DM** is the result of interactions of **Genetic, Environmental**, and **Immunologic Factors** that ultimately lead to the **destruction of the pancreatic beta cells** and **insulin deficiency**.
- Type 1 DM results from **Autoimmune Beta Cell Destruction**, and most, but not all, individuals have evidence of Islet-directed Autoimmunity.
- Individuals with a Genetic Susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years.
- This autoimmune process is thought to be triggered by an Infectious or Environmental Stimulus and to be sustained by a **Beta Cell—specific Molecule.**
- Features of diabetes do not become evident until a majority of beta cells are destroyed (**70 - 80%**).
- After the initial clinical presentation of type 1 DM, a "**honeymoon**" **phase** may ensue in the first **1 or 2 years** after the onset of diabetes.
- During which time Glycemic control is achieved with Modest Doses of Insulin or, rarely, Insulin is Not Needed.
- However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys remaining beta cells, and the individual becomes insulin deficient.
- Some individuals with long-standing type 1 diabetes produce a small amount of insulin (As reflected by **C-peptide production**)
- And some individuals have insulin-positive cells in the pancreas at autopsy.
- Islet Cell Autoantibodies (**ICAs**) are present in the majority of individuals (**>85%**) diagnosed with New-onset type 1 DM.



Type II DM

- Type 2 DM is characterized by Impaired Insulin Secretion, Insulin Resistance, Excessive Hepatic Glucose Production, and Abnormal Fat Metabolism. Insulin Resistance and Abnormal Insulin Secretion are central to the development of **Type II DM.**

- Although the primary defect is controversial, most studies support the view that Insulin Resistance precedes an Insulin Secretory Defect but that diabetes develops only when insulin secretion becomes inadequate.
- In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output
- In Asian, African, and Latin American), DM that is **Ketosis Prone** (Often Obese) or **Ketosis-Resistant** (Often Lean) is commonly seen.
- The disease is polygenic and multifactorial, since in addition to Genetic Susceptibility, **Environmental Factors** (Such as Obesity, Nutrition, and Physical Activity) modulate the phenotype.
- Even though, HLA gene Abnormality is speculated in type I DM, the genes that predispose to type 2 DM are incompletely identified. Genetic Polymorphisms associated with type 2 diabetes have also been found

Management of DM

Principle of management

- Medical Nutrition Therapy (MNT)
- Pharmacologic treatment with insulin or oral hypoglycemic drugs
- Diabetics education about
    - Diet
        - When they feel hypoglycemia, they have to take table sugar or candy (they should have candy in their pocket)
        - Avoid alcohol; which expose to comorbidities like HTN and patient may miss his/her drug because of alcohol intoxication
        - Take mixed food; variation between breakfast and dinner if possible
        - Take vegetable
        - Avoid refined food since they have high sugar content
        - Avoid raw meat and fat intake
    - DM natural history
    - Type and Route of administration of Insulin.
        - In our setup, patients differentiate regular insulin and NPH based on color. (regular insulin = ውሃው፣ ውሃ የሚመስለው and NPH = ወተቱ ፣ ወተት መልኩ)

          Administration
        - Morning → periumbilical
        - Evening → extremities
            - This variation is because of exercise increase insulin absorption (extremities involved in daytime activity)
    - storage of insulin

  - Self-blood glucose monitoring (SBGM)
  - Sign and symptoms of hypoglycemia and hyperglycemia
  - Stop smoking and Moderation of alcohol intake
  - Exercise
  - Foot care
- Screening for micro and macro vascular complications
- Treatment of infections (e.g. UTI, Pneumonia, vulvovaginitis/candidiasis/)
- Follow up

Non pharmacologic treatment for both Type I and Type II DM

1. Medical Nutrition Therapy (MNT): general guidance

Principles of nutritional therapy

- Focus on supporting the patient on choosing healthy eating behaviors.
- Consider the literacy of the individual, access to food, and willingness.
- Try to maintain the pleasure of eating as much as possible
- Respect and address the individual preferences, cultural, and religious choices.
- Be nonjudgmental
- Be practical
- Limit food choices when only supported by scientific evidences
- Help overweight and obese individuals to decrease body weight
- Help attain individualized glycemic, blood pressure, and lipid goals.

General advice

- Avoid refined sugars: soft drinks with sugar, or adding sugar/honey to teas/other drinks.
- Carbohydrate
  - Reduce overall carbohydrate intake
  - Carbohydrate sources high in fiber and minimally processed are preferred: whole grains, non-starchy vegetables, fruits, and dairy products Be encouraged to have complex carbohydrates
- Fat
  - Reduce saturated fat (animal fat) intake: butter, ghee, fatty cuts of meat, cheese.
  - Reduce Trans-fat (hydrogenated oil): solidified vegetable oils
  - Mono-saturated and polyunsaturated vegetable oils are preferred
- Protein
  - Should be left to the individual choice.
  - When there is CKD, reduction (not stopping) protein intake.
- Sweetened beverages
  - Individuals who have had the habit sugar added beverages, taking low-calorie or nonnutritive- beverages can serve as short-term transition. However, they should be encouraged to replace with water intake.

2. Exercise

- Regular moderate-intensity aerobic physical activity: for at least 30 minutes at least 5 days a week (at least 150 min/week)
  Encourage resistance training 3 times per week.

3. **Weight management**

- For obese and overweight individuals
  - Eating plans (focusing on reduction of overall carbohydrate intake) and exercise

4. **Stop smoking**
5. **Moderation of alcohol intake**

- A maximum 1 drink for women and 2 drinks for men.
  - One drink is roughly equivalent to a bottle of beer, a glass of wine, or a unit of spirit.

F. **Self-blood glucose monitoring (SBGM)**

G. **Screening for micro and macro vascular complications**

Pharmacologic treatment → **management of blood sugar**

Target blood glucose

- Target should be **individualized.**
- In young patients with recent diagnosis, without significant chronic complications, tight glycemic control should be encouraged.
- Individuals for whom less stringent (HbA1C < 8 to 8.5%) should be considered
  - History of severe hypoglycemia
  - The elderly and those limited life expectancy
  - Established cardiovascular disease
  - Advanced microvascular disease e.g. advanced chronic kidney disease
  - Significant comorbid conditions e.g. liver disease, malignancy
  - Long duration of diabetes

Target in most non-pregnant adults without significant comorbidities:[12]

Table; Glycemic targets for non-pregnant adults without significant comorbidities

	TARGET	Remark
FBS	**100 -130mg/dl**	**In young, highly motivated, well supported** patients a **HA1C target <6.5%** and **FBS of 80-130mg/dl** can be aimed, if it can be achieved without causing recurrent hypoglycemia.
HbA1C	< 7.5%	

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[12] Reference from 2021 STG for General Hospitals in Ethiopia. According to Harrison 20th edition, the target range of glycemic control is RBS < 180mg/dl, FBS = 80 - 130mg/dl, HbA1c < 7.0 %. As recommended by the ADA; goals should be individualized for each patient with a different goal for different patients. HbA1c is primary goal.

Post meal glucose level	**< 180mg/dl**	**Done 1-2hr from the beginning of meal**

Treatment of Type - I DM

Pharmacologic

- **Insulin** is the main stay of treatment in type I diabetes

Table; properties of insulin preparations

PREPARATIONS		ONSET (hr)	PEAK (hr)	DURATION (hr)
Short acting	**Regular**	0.5-1	2-4	6-8
	Lispro	0.25	1	3-4
	Aspart			
	Glulisine			
Intermediate acting	**NPH** a.k.a Isophane NPH stands for Neutral Protamine Hagedorn	1-3	6-8	12-16
Long acting	Glargine	1	None	11-24
	Detemir	1	3-9	6-23

- **Insulin regimen in type I Diabetes Mellitus:**

1) Conventional insulin therapy

- It encompasses simpler non-physiologic insulin regimens.
- These include single daily injections, or two injections per day (including a combination short-acting and -NPH insulin)
- **The conventional insulin regimen uses a mixture of regular insulin and NPH administered before breakfast and before the evening meal**
- **2/3rd of the total daily dose is injected in the morning and 1/3rd in the evening.**
- **Approximately 2/3rd of each injection comprises NPH and 1/3rd is regular insulin**

A) **Intensive insulin therapy**

- It describes treatment with >3 injections/day or continuous insulin infusion
- It requires frequent monitoring of blood sugar: fasting, before lunch, before dinner & before bed.
- It also requires the following
  - Counting and recording carbohydrates.
  - Adjusting insulin doses in response to given glucose patterns.
  - Coordinating diet, exercise, and insulin therapy.
  - Responding appropriately to hypoglycemia

B) **Designing insulin therapy**

- Total insulin dose per day **Initiation, 0.2 to 0.4 units/kg/day**
- **Maintenance → highly variable roughly 0.6 to 0.7 units/kg/day**
- For doses above 20units divided in to two (about 2/3 in the morning and 1/3 in the evening)
- Regimen options-with NPH and regular insulin

- **Preferred regimen: NPH with premeal regular insulin**
  - **NPH** before breakfast and at bed time PLUS
  - **Regular Insulin** three times daily injection: before breakfast, lunch, and dinner
- **Other options:** If the patient work, routines, social circumstances, and support do not allow the patient to do the preferred regimen
  - **Mixed NPH and regular insulin → 70/30 (70% NPH & 30% regular)**
  - NPH with pre-breakfast and pre-dinner regular insulin
  - Twice daily NPH injections only: Before breakfast and before bedtime

Treatment of Type - II DM

Blood glucose lowering medicines

First line: Metformin

- ✓ Initial dose 500mg to 1000mg/day daily or in two divided doses with meals.
- ✓ Titrate dose **every two weeks** depending on the FBS
- ✓ Maximum dose = **2000mg/day (1000mg BID)**
  - Metformin is contraindicated in patients with advanced CKD (eGFR <30ml/min), advanced CLD, and hypoxia.

Alternative to Metformin

- ✓ If Metformin is contraindicated a **sulfonylurea** can be started
- ✓ **Basal insulin** can also be started as an alternative (see for indications for starting insulin in type 2 diabetes below)

Add on to Metformin: If glycemic target is not achieved by metformin alone after **three months**, add either of the following.

- ✓ **Sulfonylureas**: Glibenclamide, Glimepiride, Gliclazide OR
- ✓ **Basal insulin**

Initiating two oral agents at diagnosis

- ✓ Patients with **severe hyperglycemia at presentation** (HbA1C >10% or FBS >250 mg/dl or RBS consistently >300 mg/d) **and prefer oral agents** than insulin, need to be started on a **combination of metformin and sulfonylurea.**

- **Sulfonylureas**
  - ✓ **Glibenclamide (Glyburide)**
    - Starting dose is 2.5-5mg/day, 30 minutes before breakfast.
    - Titrate dose slowly to maximum of 20mg/day
    - When 10mg/day is needed, divide the total dose into two, with the larger dose in the morning.
    - Avoid in the elderly and patients with renal impairment.
  - ✓ **Glimepiride**
    - Starting dose is 1-2 mg/day, 30 minutes before breakfast.
    - Titrate dose slowly to maximum of 8mg/day
  - ✓ **Gliclazide, modified release**
    - Starting dose 30mg/day
    - Titrate the dose slowly to a maximum dose 120mg/day

The major side effect of sulfonylureas is hypoglycemia.

- Individuals should be educated about the risk, manifestations, prevention and treatment of hypoglycemia.
- Sulfonylureas should be avoided or given at lower doses in individuals at high risk of hypoglycemia (e.g. the elderly, with significant comorbidities, history of hypoglycemia)

- **Insulin therapy in type II diabetes**
  - ✓ **Indications for insulin therapy**
    - Failure to control blood glucose with oral medicines
    - Temporary use for major stress, e.g. surgery, medical illness
    - Severe kidney or liver failure
    - Pregnancy
    - In patients difficult to distinguish type 1 from type 2 diabetes
    - Ketonuria
    - Unexplained weight loss accompanied by poorly controlled blood sugar
    - Initial therapy for a patient presenting with very high blood sugar
      - HbA1C >10% or FBS >250 mg/dl or RBS consistently >300 mg/d

  - ✓ **Dosing basal insulin in type II diabetes**
    - If started on as an add on therapy to Metformin
      - Starting dose = NPH 10 units at bed time
      - A higher dose might be started for higher blood glucose
      - Dose increment 2-4 units in 3-7 days with self-monitoring of blood sugar
    - If started as a replacement for oral agents
      - Starting dose = NPH 15 -20 units at bed time
      - A higher dose might be started for higher blood glucose

    - For doses above 20units divided in to two (about 2/3 in the morning and 1/3 in the evening)
    - Dose increment 2- 4 units in 3-7 days with self-monitoring

- ✓ **Addition of prandial regular insulin**
  - Indications to start regular insulin before meal
    - If FBS is well controlled but HbA1c is above target
    - If HbA1c is above target despite increasing basal insulin to >0.5 unit/Kg/day
  - Dosing prandial regular insulin
    - Starting dose of prandial insulin: Regular insulin 4units
    - Preferred time: before the largest meal of the day
    - Dose increment 1-2 units in 2-3 days with self-monitoring of the next pre-meal_blood glucose

Other oral diabetic medications for the care of patients with type II DM.

- **Sulfonylureas or basal insulin** to be the **preferred add-on therapies next to metformin. This is mainly based on cost related factors.**
  - ✓ For patients who can afford to buy or get access to these medications, decision on which agent to add to Metformin, combine with Metformin from the beginning or sometimes start an initial treatment should be individualized based on the following factors.
    - The need for weight loss
    - Risk of hypoglycemia in the patient
    - the presence of cardiovascular disease
    - The presence of CKD.

Table; available medications in Ethiopia

Class of medication	**Available drugs and in Ethiopia**	**Clinical sates in which the drug is most beneficial**
SGLT2 inhibitors (Sodium glucose transporter -2 inhibitors)	**Dapagliflozin,** 5 or 10mg, po, daily	✚ Heart failure ✚ Early stages of CKD ✚ Compelling need to decrease the risk hypoglycemia ✚ Compelling need to decrease weight loss or reduce weight ✚ Need to improve glycemic control ✚ Additional benefit of BP lowering ✚ Avoid in advanced CKD
DPP4-inhibitors (Dipeptidyl peptidase -	✚ **Saxagliptin,** 2.5 - 5mg, po, daily ✚ **Vildagliptin,** 50mg, po, daily or BID	✚ Compelling need to decrease the risk hypoglycemia ✚ Need for intensification of glycemic control ✚ Weight neutral (no increment or significant decrement)

4 inhibitors)	Each of these drugs are also available as FDC with Metformin 500mg or 1000mg)	Dose reduction need in patients with CKD.

Management of other cardiovascular (CV)risks

1) **Cardiovascular risk calculation**

All patients 10-year cardiovascular risk factor needs to be calculated

2) **Blood pressure management** (See section on hypertension from chapter 1; click here → Hypertension (የደም ግፊት) and HHD)

- Target blood pressure: <130/80mmHg
- First line if there is proteinuria: ACE inhibitors or ARBs
- First line if no proteinuria: CCB, thiazide diuretics or ACE inhibitors or ARBs.
- Preferred two drug combinations for patients with proteinuria
    - ACE inhibitors/ARB + CCB
    - ACE inhibitors/ARB + Thiazide diuretics
- Preferred combination for patients with no proteinuria
    - CCB + ACE inhibitors/ARB
    - CCB + Thiazide diuretics
- Preferred 3 drug combinations
    - ACE inhibitors/ARB + CCB + Thiazide diuretic

3) **Lipid lowering therapy**

Indications

- Age above 40 without additional CV risk
    - Start moderate intensity statin
    - Make it high intensity if there is additional CV risk
- All ages with a history of cardiovascular risk
    - Start high intensity statin
- Age 20-39 years with one or more CV risk factor

4) **Antiplatelet therapy**

- **Aspirin (81-162mg/day)**
    - It is only indicated for patients who have CV disease (coronary artery disease, ischemic stroke or peripheral arterial disease)

Screening and management of Chronic complications of diabetes

- Prevention, detection, delaying progression and supportive management of these complications is an important part of care of patients with diabetes

- Prevention of these complications can be achieved through optimal glycemic control, optimal blood pressure management, lipid control, quitting smoking and maintaining a healthy life style.

Table: screening and management of chronic complication of diabetes

	Initial screening	Follow up screening	Prevention & Treatment

Nephropathy	T1DM → after 5 years
	T2DM → at diagnosis
	Screening tool:
	  U/A→ Albuminuria
	  Creatinine, eGFR
		No nephropathy → annually
		Nephropathy → 2x/yr
		if eGFR < 30ml/min consult nephrologist together with endocrinologist
			Optimize glycemic control
			Optimize BP control
			ACEi/ARB for proteinuria

Retinopathy	T1DM → after 5 year T2DM → at diagnosis Before and at time of pregnancy Screening tool: Dilated eye examination by ophthalmologist	No retinopathy → in 1-2yr Retinopathy →1yr Sight threatening retinopathy needs more frequent evaluation	Optimize glycemic control Optimize BP control Optimize lipid control Pan retinal laser photocoagulation Intra vitreous injections of anti-vascular endothelial growth factor ASA is not recommended in patients with retinopathy

Neuropathy	T1DM → after 5 years
	T2DM → at diagnosis
	Screening tool
	  Careful history
	  Temperature/ pinprick & vibration sensation
	  10-g monofilament testing
		Annually	Optimize glycemic control
			Symptomatic management
			Painful neuropathy
			Amitriptyline: 12.5-50mg PO/bedtime
			Gastroparesis
			Plasil,10mg PO, TID (syrup preferred)
			Alternatives (2nd line)
			Domperidone 10mg PO TID
			Erythromycin syrup, 50-250mg, TID
			Diabetic diarrhea
			Symptomatic treatment
			  Loperamide 2-4mg, PO, TID or QID or
			  Codeine 30mg, PO, TID or QID
			Treatment of bacterial overgrowth: Antibiotics for 7-10days
			  Norfloxacin 400mg, PO, BID Or
			  Metronidazole 500mg, PO, TID PLUS
			  Cephalexin 500mg, PO, TID or
			  Cotrimoxazole 960mg BID
			Postural hypotension
			Change posture slowly
			Elevate head by 10-20⁰
			Dorsiflexion of feet and handgrip (before standing
			Tensing legs by crossing (when standing)

			Bladder dysfunction Remove drugs which worsen it (Amitriptyline, CCB) Strict voluntary voiding schedule Crede maneuver (lower abdominal pressure by hands) If severe: Self intermittent catheterization **Erectile dysfunction** Use PDE5 inhibitors Sildenafil 25 -100mg (start with 50mg) Vardenafil 10-20mg Tadalafil 10-20mg If refractory Tadalafil 2.5-5mg/daily Take 01hr before sexual encounter On empty stomach Avoid use with nitrates
Diabetic foot	Initial visit Screening tools Assessment of skin & foot deformities Neurologic exam PAD evaluation	Every visit	Look at diabetic foot ulcer section below

Follow up on Chronic OPD

- Glycemic Control → The ABCs
  - A → HbA1C is the blood glucose check "with a memory." It allows one to determine average blood glucose control over the past 2 to 3 months. The ADA recommends an A1C below 7.
  - B→ BP, The ADA recommends a BP < 130/80.
  - C → is for cholesterol
- Escalate or deescalate medication dose based on target glucose level
- Screen and treat complication based on the above table schedule
- Look at follow up investigations above (investigation section)

10.1 Diabetic foot ulcer

Clinical features and how to write hx of Diabetic foot ulcer

History

If a known DM patient → ask the following on your HPI

- Type I DM
  - For how long he/she was diagnosed to have DM
  - Ask the dose and frequency of insulin injection. → Usually a mixture of 2/3 of NPH and 1/3 of regular insulin. From this mixture 2/3 of the dose taken in the morning and 1/3 at night.
  - Specify alternative injection sites
  - Where he/she does store their insulin→ wet sand bags or refrigerator
  - Adherent or not
  - Where was the follow up and frequency (every month, every two months….)
  - How was his/her smx's in between… improving, worsening or no change at all… if not improving or worsening what was the reason (non-adherence, wrong diagnosis ……)

Reporting format example

A known DM pt for the past 6 years or you can say 6 years back s/he was told to have DM (you can ask what was the presentation at that time and how Dx was made… no need to write on your HPI) **taking insulin injection 20 units in the morning and 10 units at night. With alternative injection sites between his/her upper arms, thighs and periumbilical area. Stores his/her insulin in wet sand bag /refrigerator/. S/he was adherent for his/her medication with regular follow up every 3 months here in our hospital.**

- Type II DM
  - For how long he/she was diagnosed to have DM
  - What medication he was taking and ask the dose and frequency of each medication. If the pt' doesn't remember or doesn't know the name of the drug ask the colour, frequency, and route of the

medication (e.g he/she was taking white coloured tablet 3 times per day).

  - Does he/she start insulin other than oral hypoglycaemic drugs? If yes what is the reason of shifting to insulin.
  - Adherent or not
  - Where was the follow up and frequency (every month, every two months….)
  - How was his/her smx's in between… improving, worsening or no change at all… if not improving or worsening what was the reason (non-adherence, wrong diagnosis ……)

Reporting format example

A known DM pt for the past 6 years or you can say 6 years back he was told to have DM **(you can ask what was the presentation at that time and how Dx was made… no need to write on your HPI)** **On metformin 500 mg, PO, daily . He was adherent for his medication with regular follow up every 3 months here in our hospital.**

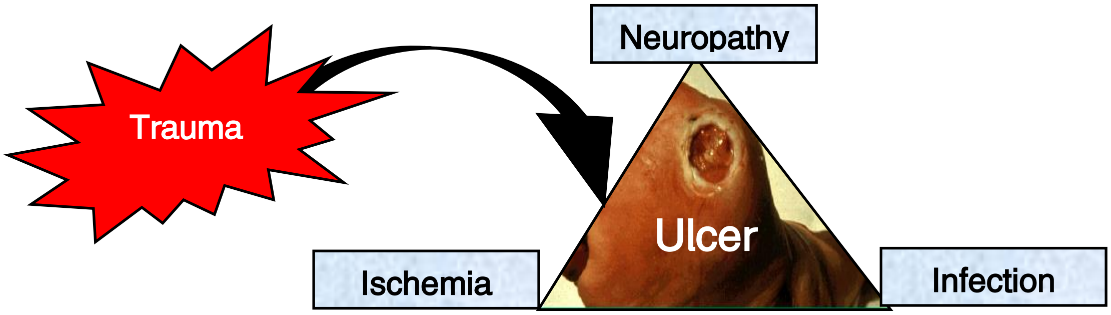
Then ask clinical features of foot ulcer

- **intermittent claudication**
  - Left/right calf stabbing type of pain which radiates to toes → usually after waking of >200 meters
  - Occur while walking and relieved by massage, sitting or lying down
- Numbness which spread upwards usually up to the knees (ask with in how many days it reaches the knee).
- Burning sensation (over where?) which worsen by walking and relieved by massage, cold water and pain killer
- Foot swelling→ where?
  - Gradual in onset
  - Overlying skin colour change
    - Blackish discoloration of overlying skin→ up to where? Subside or not?
  - Painful or painless?
  - Ulcerated or not?
  - If ulcerated
    - When does it ulcerate?
    - What is the colour of discharge?
    - Size→ Usually small in size, which increase gradually (with in how many days does it attain it's current size)
- Associated smx's like fever, chills, palpitation, headache…. when does they occur and frequency of smx's within the day (morning, afternoon, night, throw-out the day)?

Risk factors

- Long standing DM → *Diabetes >10 years' Duration*
- Poor glycemic control
- Wearing unfit shoes
- Waking bare foot
- Unclean foot
- Trauma
- Male Sex
- Abnormal Structure of Foot (Bony Abnormalities, Callus, Thickened Nails)
- PAD
- Smoking
- History of Previous Ulcer or Amputation
- Concurrent DM complications
    - Chronic sensory motor **neuropathy or autonomic neuropathy**
    - Vascular disease like **ischemia**
    - **Infection**
    - Impaired immune function

Diabetic foot Triad



Diabetic Neuropathy (80% of pts)

- 7% annual risk of ulceration
- Sensory, motor, and autonomic
- **Decrease pain sensation and perception of pressure**
- Ms imbalance leading to deformities
    - **Hammer toes, Claw toes Prominent metatarsal heads**
- **Reduced sweating, dry skin, and development of cracks and fissures**

Peripheral Vascular Disease

- Increased incidence by 2-4fold
- Promotes development of **critical limb ischemia, poor wound healing and tissue loss**

N.B Complications of DM like Diabetic foot ulcer are common in Type II DM than Type I DM

Complication of Diabetic foot ulcer

- Cellulitis
- Abscess formation
- Joint sepsis
- Osteomyelitis
- Gangrene and Amputation→ DM is the most common cause of non-traumatic foot amputation

Sample history

Chief compliant

Left foot ulceration of 1-month duration

HPI

A known DM patient for the past 8 years on metformin 500 mg, PO, daily for 5 years and she was adherent for her medication with regular follow up every 3 months here in Black Lion Hospital. For the last 3 years insulin was added because she was told that her blood glucose level was not well controlled by oral hypoglycemic drugs. Currently she took 24 units of insulin in the morning and 12 units at night with alternative injection sites between her upper arms, thighs and periumbilical area. Stores her insulin in refrigerator.

She was relatively healthy until three months ago at which time she started to experience a gradual onset of left calf stabbing pain which radiates to the toes and numbness of both feet. Both symptoms were intermittent occurring mainly when walking and relived by massaging of the legs, sitting and lying down. The numbness started to spread upwards from the toes and involved the knees within 2 weeks duration associated with burning sensation of the left sole of the foot which was constant but increased in intensity when walking while painkillers and massaging in cold water eased the pain. Following this she came to Black Lion Hospital. Since no bed was available, she was scheduled to come three weeks later and was sent home.

she missed her appointment due to unknown reason and around one month before admission, she noticed swelling of the left foot and a small black discoloration on the plantar surface of the left big toe. The swelling involved up to the knee but subsided after 4 days of constant massaging while the black discoloration of the toe increased in size and ulcerated one week later with non-foul-smelling blood mixed pussy discharge. The ulcer was small at first but within the following two weeks it enlarged constantly involving the whole plantar surface of the left big toe. One week before admission she started experiencing a sudden onset of intermittent fever accompanied by sweating, chills, rigor, palpitations and numbing global headache.

Following this She came to black lion hospital emergency OPD and was admitted to B8 ward on the same day.

- *Ask those +ve and -ve statements listed on the sample hx of a DM patient above.*

- She has a **history of foot ulcer two years ago** on the same toe. She went to Ras Desta Hospital and was advised to have an amputation of the toe but she refused and was discharged. But the patient claims that after two weeks of washing the foot with salt water the ulcer subsided and disappeared.
- She has **history of blurring of vision 8 years back** at the time of diagnosis of the diabetes. Laser eye surgery was done at Menelik hospital on the left eye but the patient refused for the right eye due to discomfort. Following that the eye sight on the left eye corrected but on the right eye, the blurring of vision and shadowing progressed to total blindness.
- She wears well fitted shoes and doesn't walk bare foot *(RF)*
- She dry skin of foot after washing leg, check between toes, and she adds lotion to leg (unclean foot is RF)
- No hx of Leg trauma (traumatic ulcer →DDX)

Physical examination (pertinent findings)

- ✓ **Assess all pertinent findings listed above for DM pt'**
- ✓ Arterial examination especially posterior tibial artery and dorsalis pedis artery (asses for PAD)
- ✓ Do full musculoskeletal examination (look, feel, move and measure)
- ✓ Characterize the ulcer
    - Location → *Great Toe and MTP areas are most common.* Toes (51%), Plantar metatarsal head (28%), Dorsum of foot (14%), multiple ulcer (7%)
    - Single or multiple
    - Margin → regular/irregular, sloughing or not
    - Type and colour of discharge
    - Surrounding skin colour change (gangrene) and erythema (measure the size)
    - Compare temperature with surrounding skin
    - Surrounding tenderness
    - Size (length and diameter i.e. "X" by "Y" cm). Wound Depth should be determined by inspection and probing with a blunt-tipped sterile instrument.
    - Floor bleed during touching or not
    - Is the bone visible or not?

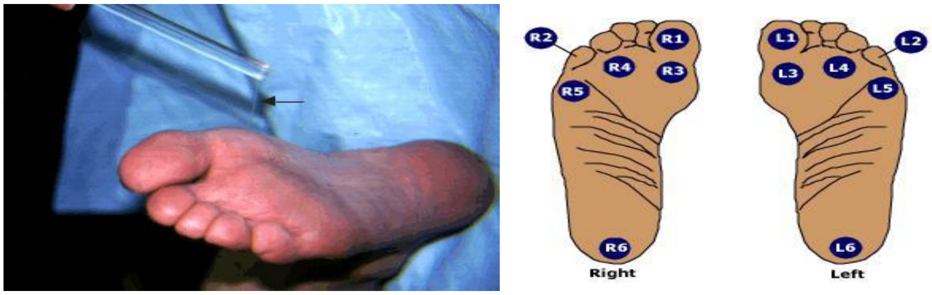
- ✓ Assess systemic cxn like fever
- ✓ Measure ABI (ankle brachial index)

$$\mathbf{ABI} = \frac{\textbf{SBP of ankle}}{\textbf{SBP OF Brackial artery}} = \mathbf{0.9 - 1.1}$$

- ➢ SBP of ankle measured by Doppler ultrasound guided BP measurement but SBP of arm can be measured by sphygmomanometer (by any BP cuff available in the ward)
- ➢ ABI < 0.9 is evidence for PAD, > 1.1 is evidence for vessel wall calcification

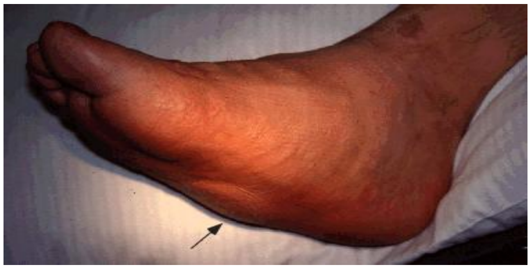
Evaluation for the foot at risk

- ✓ Look for PAD → Foot Pulses, Doppler
- ✓ Look for Neuropathy → Tuning Fork, Monofilament



Picture; left) *Monofilament Testing, right) Monofilament Testing Areas*

- ✓ Anatomic Deformities → Charcot's Foot, Hammer Toes, Clawed Toes



Picture; Charcot foot

DDX for foot ulceration in DM patient

1. Diabetic foot ulcer
2. PAD → `refer nitsibin under CHF (click here →` Peripheral Arterial Disease (Chronic Arterial Insufficiency)
3. Leprosy → Anaesthetic skin lesion, swelling
4. Venous ulcer → usually after varicose vein
5. Arterial ulcer

6. Haemolytic anemia → non healing ulcer from SCA or autoimmune haemolytic anemia
7. Gumatous ulcer
8. Traumatic ulcer
9. Cellulitis
10. TB (mycobacterium ulcerans) → rare ulcer which is known as Bruli ulcer
11. Madura foot
12. Anthrax
13. Neuropathic ulcer (peripheral neuropathy)
14. Tropical ulcer (pressure ulcer)
15. Malignant ulcer
16. Specific ulcer
17. SCC (marjolin ulcer)

IX

1) Blood sugar level → hyperglycaemia
2) Discharge analysis & culture for infection

- Infected ulcer is a clinical diagnosis, since superficial culture of any ulceration will likely find multiple possible bacterial species.
- The infection surrounding the foot ulcer is often the **result of multiple organisms (Gram +ve, Gram -ve and Anaerobes),** And Gas Gangrene may develop in the absence of Clostridial Infection.
- Cultures taken from the Surface of the ulcer are not helpful. But, **A culture from the debrided ulcer base or from purulent drainage or aspiration of the wound is the most helpful.**

3) U/A → glucosuria, ketonuria
4) CBC → leucocytosis
5) X-ray of the involved area if bone is involved (osteomyelitis)
6) **MRI** of the foot may be the most specific modality
7) Doppler ultrasound of supplying artery to see its patency
8) Pancreatic function test → amylase
9) If Surgical Debridement is necessary → Bone Biopsy and Culture
10) Other IX listed in DM → refer DM

Discussion

- Diabetic foot ulcers are Slowly healing plantar ulcers that result from apparently insignificant trauma
- The lifetime risk of a foot ulcer in patients with diabetes (type 1 or 2) may be as high as 25 %.
- Diabetic foot ulcers are a major cause of morbidity and mortality, accounting for approximately 2/3rd of all nontraumatic amputations performed in the United States

- Left untreated, superficial ulcers may penetrate to underlying tissues, leading to complications including cellulitis, abscess formation, joint sepsis, and osteomyelitis
- Gangrene may occur, and amputation may be required in severe cases.
- To varying degrees, the diabetic foot is characterized by the combination of chronic sensorimotor neuropathy, vascular disease, autonomic neuropathy, and impaired immune function
- Once an ulcer has formed, it should be treated aggressively with antibiotics, appropriate local wound care, and debridement of necrotic tissue

Ulcer Classification

- The first step in managing diabetic foot ulcers is assessing, grading, and classifying the ulcer.
- Classification is **based upon** clinical evaluation of the **extent and depth of the ulcer** and the **presence of infection or ischemia**, which determine the nature and intensity of treatment.
- **To assess for ischemia**, all patients with diabetic foot ulcers should have **ankle-brachial index (ABI)** and toe pressure measurements.
- **There are many Classification systems of diabetic foot ulcer.** We will see common ones here.
  - **Wagner** classification system
  - **University of Texas** classification system
  - **IDSA** classification system
  - **WIFI** classification system
  - **PEDIS** classification system

    (where; **IWGDF** = International Working Group on the Diabetic Foot, **IDSA** = Infectious disease society of America, **WIFI** = Wound/Ischemia/Foot Infection, **PEDIS** = Perfusion, extent, depth, infection, and sensation)

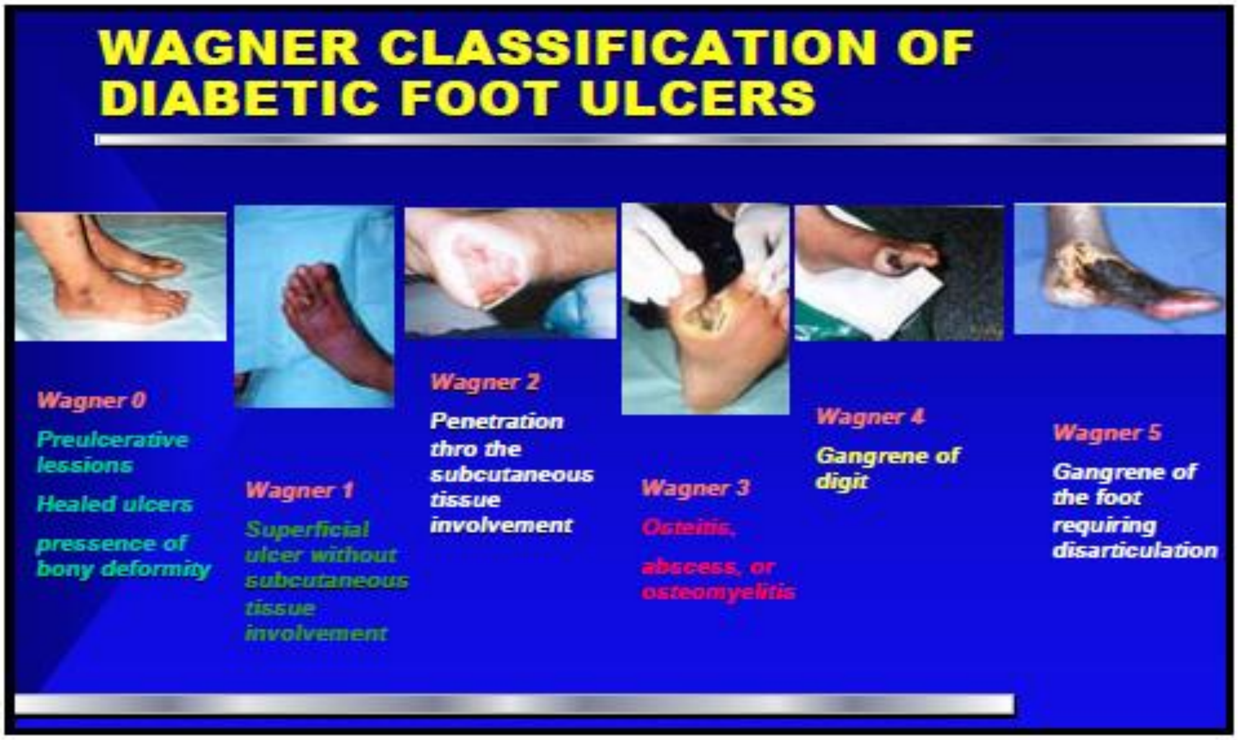
N.B.

- **Only two classification systems have been developed that provide stratification that aligns to clinical decision-making: IWGDF/IDSA and WIFI.**
- **whilst the IWGDF/IDSA is incorporated into the WIFI, in situations where only infection is being assessed and equipment is not available to use WIFI, the IWGDF/IDSA infection classification can stand alone.**
- **IDSA is the recommended classification system for management and clinical use in our setup.**

✓ Wagner classification system

- It is an early and often still used classification system at hyperbaric-based wound healing centers was originally proposed by Wagner.
- This classification was based upon clinical evaluation (depth of ulcer and presence of necrosis) alone and did not account for variability in the vascular status of the foot.
- The Wagner system is predictive of poor outcome, but only up to grade 3.

- Even though we are using in our setup, it is outdated from use in most countries because it is a local grading system which doesn't consider systemic conditions like loss of protective sensation, infection, and ischemia.
- It includes:
  - Grade 1: Skin and subcutaneous tissue
  - Grade 2: To bone
  - Grade 3: Abscess or osteitis
  - Grade 4: Partial foot gangrene
  - Grade 5: Whole foot gangrene



WAGNER CLASSIFICATION OF DIABETIC FOOT ULCERS

Wagner 0

Preulcerative lessions

Healed ulcers

pressence of bony deformity

Wagner 1

Superficial ulcer without subcutaneous tissue involvement

Wagner 2

Penetration thro the subcutaneous tissue involvement

Wagner 3

Osteitis,

abscess, or osteomyelitis

Wagner 4

Gangrene of digit

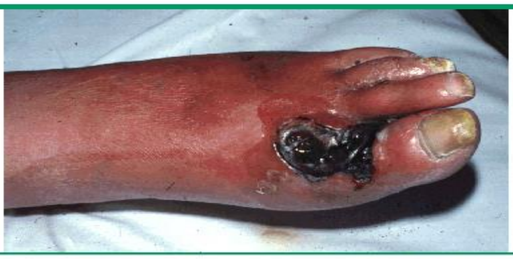
Wagner 5

Gangrene of the foot requiring disarticulation

✓ University of Texas system

- An update to the Wagner system was introduced at the University of Texas (UT), San Antonio in the United States.
- While similar to Wagner in its first three categories, this later system eliminated grades 4 and 5 and added stages A to D for each of the grades.
- The UT system was the first diabetic foot ulcer classification to be validated.
- Stage:
  - Stage A: Noninfected
  - Stage B: Infected
  - Stage C: Ischemic
  - Stage D: Infected and ischemic

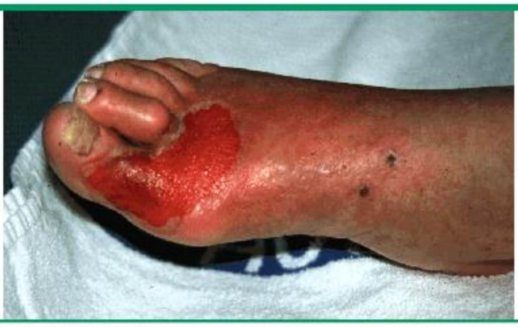
Infected and ischemic diabetic foot ulcer



Foot from a diabetic patient with an ulcer that extends to the deep layers with signs of local infection, cellulitis, and necrosis. This lesion healed completely after a hospital stay involving excision of necrotic tissue but no amputation.

- **Grade**
  - ✓ Grade 0: Pre- or post-ulcerative (Stages A to D)

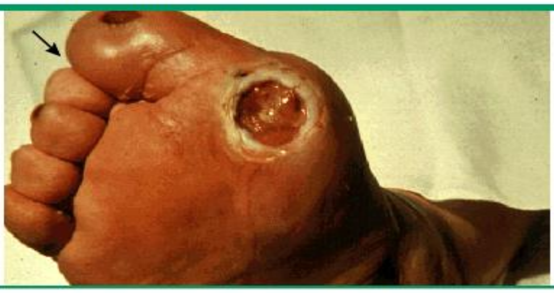
Superficial diabetic foot ulcer



Foot from a diabetic patient showing a superficial ulcer that involves a partial thickness of the skin but no involvement of the underlying tissues. This lesion healed quickly with rest and local foot care.

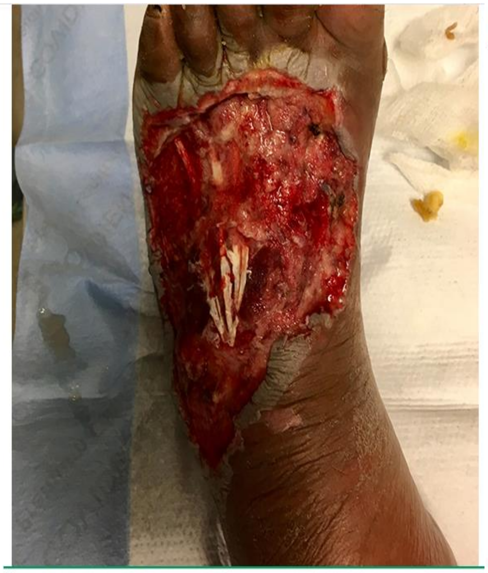
- ✓ Grade 1: Full-thickness ulcer not involving tendon, capsule, or bone (Stages A to D)

Full thickness diabetic foot ulcer



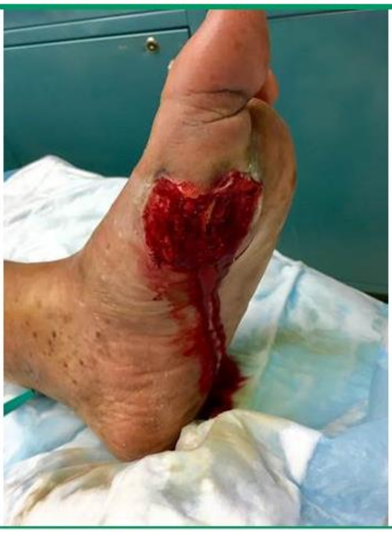
Foot from a diabetic patient with a penetrating neuropathic ulcer that is not associated with abscess formation or bone involvement. The toes have begun to claw (ie, extension deformity at the metatarsal phalangeal joint and flexion deformity at the proximal interphalangeal joint) because the pull of the extensor digitorum longus, an extrinsic muscle in the anterior compartment of the leg, overpowers the neuropathy-induced weakness of the intrinsic foot muscles. The proximal phalanges will eventually sublux, or even dislocate, dorsally. As the deformities progress, the metatarsal fat pad will migrate distally and the toes will lose the ability to effectively plantarflex and offload the metatarsal heads. The combined effect increases pressure under the metatarsal heads, predisposing to ulcer formation.

- ✓ Grade 2: Tendon or capsular involvement without bone palpable (Stages A to D)

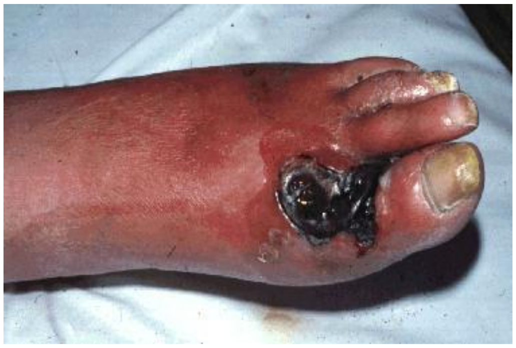


Dorsal diabetic foot wound following debridement of necrotizing streptococcal infection with exposed tendon and joint capsule.

Plantar neuropathic diabetic foot wound

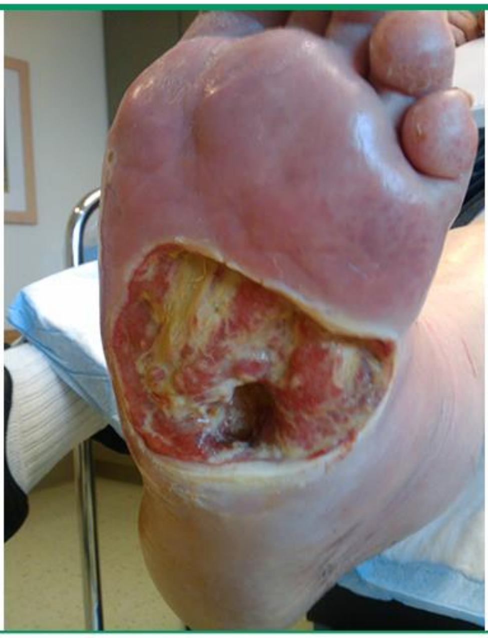


Plantar neuropathic diabetic foot wound following deroofing of bulla with exposed tendon.

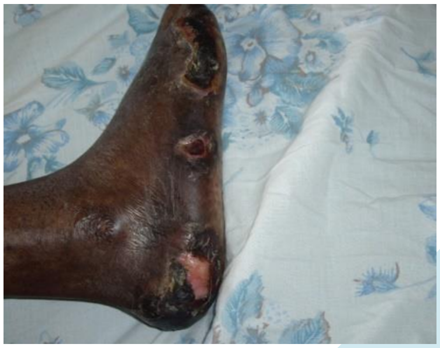


- ✓ Grade 3: Probes to bone (Stages A to D)

Deep diabetic foot ulcer involving bone



The patient presented with a fluctuant eschar on the plantar surface of the foot. The abscess was unroofed and drained and, following debridement, exposed bone was apparent at the base of the wound.



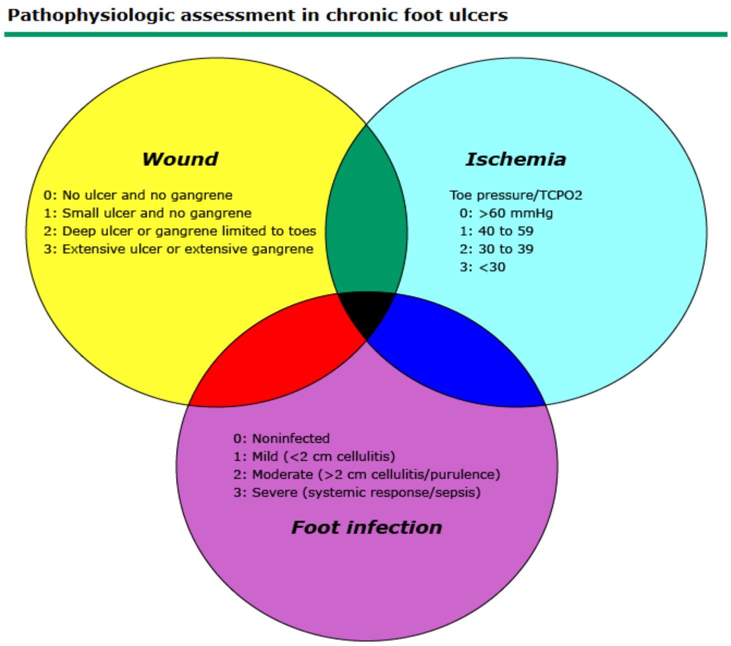
3. IDSA classification system

- IWGDF/ISDA classification consists of 4 grades of severity for diabetic foot infection.
- It was originally developed as part of the PEDIS classification for research purposes and is **used as a guideline for management, in particular to identify which patients required hospital admission for IV antibiotics.**
- It has also been validated for risk of both major and minor amputation.

Table. IWGDF/IDSA classification System

Clinical manifestations	Infection severity	PEDIS grade
Wound lacking purulence or **No manifestations of inflammation**	Uninfected	1
Presence of ≥2 **manifestations of inflammation** (purulence, or erythema, tenderness, warmth, or induration) Any **cellulitis/erythema extends ≤2cm around the ulcer** **infection is limited to the skin or superficial subcutaneous tissues** **no other local complications or systemic illness**	Mild	2
Infection (as above) in a patient who is **systemically well and metabolically stable** but **which has ≥1 of the following** characteristics: 1) cellulitis extending >2cm 2) lymphangitic streaking 3) spread beneath the superficial fascia 4) deep tissue abscess 5) gangrene 6) involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient **with systemic toxicity or metabolic instability** (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia /DKA or HHS/, or azotemia)	Severe	4

4. Threatened limb classification: Wound/Ischemia/Foot Infection (WIFI) classification system


Pathophysiologic assessment in chronic foot ulcers
Wound
0: No ulcer and no gangrene
1: Small ulcer and no gangrene
2: Deep ulcer or gangrene limited to toes
3: Extensive ulcer or extensive gangrene
Ischemia
Toe pressure/TCPO2
0: >60 mmHg
1: 40 to 59
2: 30 to 39
3: <30
0: Noninfected
1: Mild (<2 cm cellulitis)
2: Moderate (>2 cm cellulitis/purulence)
3: Severe (systemic response/sepsis)
Foot infection

Figure; WIFI classification system;

5. PEDIS classification system.

- PEDIS stands for **Perfusion, extent/size, depth/tissue loss, infection, and sensation**
- **It is primarily used for research purposes**. and not designed for prognostic purposes. It does not include patient factors (ESRD), or either the location or the number of foot ulcers.

Management of Diabetic foot ulcer

- The optimal therapy for Foot Ulcers and Amputations is Prevention through
  - Identification of High-risk Patients
    - High-risk patients should be identified during the Routine Foot Examination performed on all patients with DM
  - Education of the Patient, and
  - Institution of Measures to Prevent Ulceration.

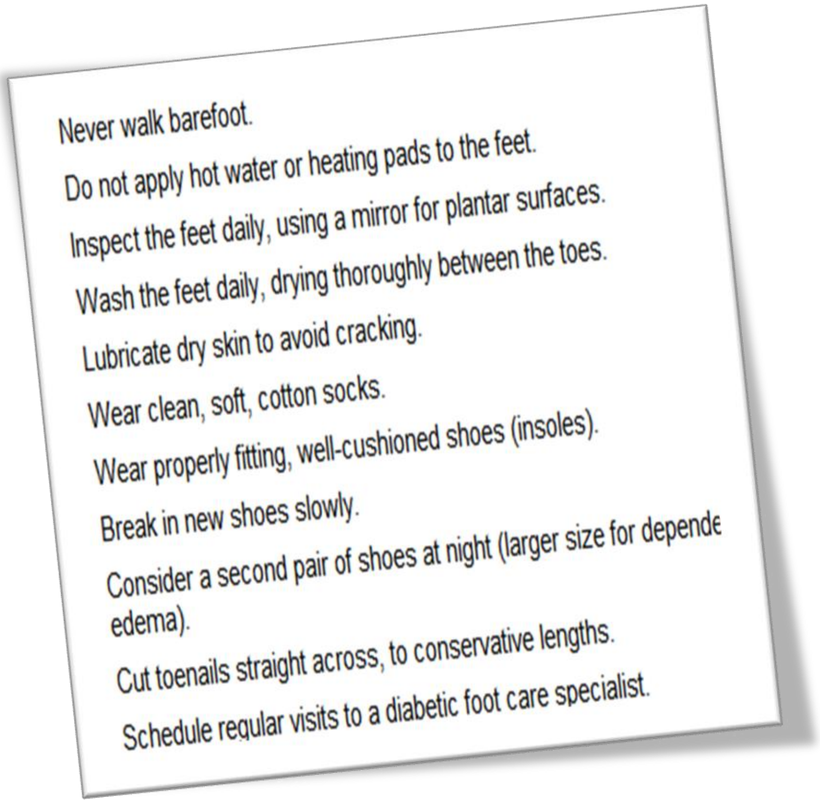
Patient Education should emphasize

- Careful selection of Footwear
- Daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma

Thoroughly inspect your feet daily, and keep them clean and dry
For DM patients "mirrors are not only for face, but also for feet beauty checkup"
ADAM.

- Daily Foot Hygiene to keep the skin clean and moist
- Avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and
- Prompt consultation with a health care provider if an abnormality arises.
- Patients at high risk for ulceration or amputation may benefit from evaluation by a Foot Care Specialist.

Foot care prescription for diabetic patients with lower extremity sensory neuropathy



Never walk barefoot.

Do not apply hot water or heating pads to the feet.

Inspect the feet daily, using a mirror for plantar surfaces.

Wash the feet daily, drying thoroughly between the toes.

Lubricate dry skin to avoid cracking.

Wear clean, soft, cotton socks.

Wear properly fitting, well-cushioned shoes (insoles).

Break in new shoes slowly.

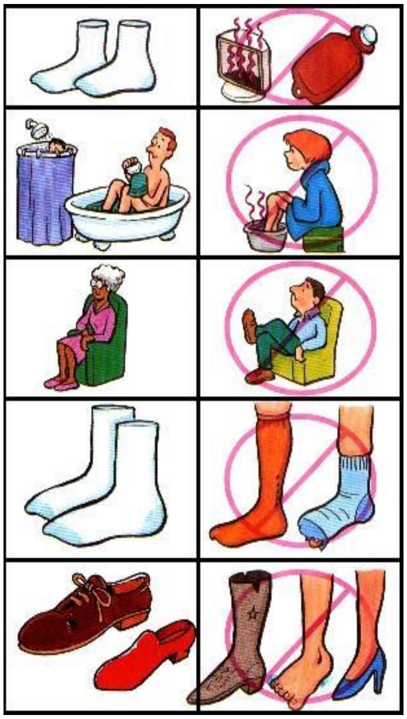
Consider a second pair of shoes at night (larger size for depende edema).

Cut toenails straight across, to conservative lengths.

Schedule regular visits to a diabetic foot care specialist.

Do's and Don'ts of foot care

Do's
Control blood sugar level



Don'ts

Don't apply hot water or irritant chemicals

Don't ignore numbness

Don't treat calluses, corns, or ingrown toenails at home

Don't cross your legs or ankles for a long period of time. Doing so can create pressure points and lead to unwanted breaks in skin

Don't go bare foot

Don't wear unfit shoes or tight socks

Don't forget you follow up at health facility

etc.

- Interventions directed at Risk Factor Modification include
  - Orthotic Shoes and Devices
  - Callus Management
  - Nail Care and
  - Prophylactic Measures to reduce Increased Skin Pressure from Abnormal Bony Architecture.
- Attention to other Risk Factors for Vascular Disease (Smoking, Dyslipidemia, Hypertension) and Improved Glycemic Control are also important.
  - One of the biggest threats to the feet is smoking!
  - Smoking affects small blood vessels by decreasing their blood flow to the feet making wounds heal slower.
  - Cessation of smoking is a good way to decrease the likelihood serious problems, such as amputation.

- Despite preventive measures, Foot Ulceration and Infection are common and represent a serious problem.
- Due to the Multifactorial Pathogenesis of lower extremity ulcers, Management of these lesions is multidisciplinary and often demands expertise in
  - Orthopedics
  - Vascular Surgery
  - Endocrinology
  - Podiatry and
  - Infectious Diseases.

ADA recommend 6 Interventions with demonstrated efficacy in Diabetic Foot Wounds:

1) Mechanical Off-loading
2) Debridement or local wound care
3) Wound Dressings,
4) Appropriate Use of Antibiotics (treatment of infection)
5) Revascularization and
6) Limited Amputation.

I. Off-Loading

- It is the complete avoidance of weight bearing on the ulcer Which removes the mechanical trauma that retards wound healing.
- Bed Rest and a variety of Orthotic Devices or Contact Casting limit weight bearing on wounds or pressure points.

II. Surgical Debridement

- Indicated If infection surrounding the ulcer is not improving with IV antibiotics and Debridement of necrotic tissue
- It is important and effective but clear efficacy of other modalities for wound cleaning (Enzymes, Soaking, Whirlpools) is lacking.

III. Dressings

- Dressings such as Hydrocolloid Dressings promote wound healing by creating a moist environment and protecting the wound.
- Antiseptic agents should be avoided.
- Topical antibiotics are of limited value.
- Physiotherapy, Orthotic Evaluation, and Rehabilitation Should occur once the infection is controlled.

IV. Appropriate Use of Antibiotics (treatment of infection)

- **Mild or Non-limb-threatening Infections (e.g.** Cellulitis Without Ulceration) can be treated with **Oral broad-spectrum Antibiotics** (**Cephalosporin, Clindamycin or metronidazole, Amoxicillin/Clavulanate, and Fluoroquinolones**), **Local Wound Care** (Avoidance of weight bearing over the ulcer), and **Close Surveillance** for progression of infection.
- More **Severe Ulcers may require IV Antibiotics** as well as **Bed Rest** and **Local Wound Care**.
- Strict control of glycemia should be a goal.
- IV Antibiotics should provide Broad-spectrum Coverage directed toward **S. Aureus, Streptococci, Gram -ve Aerobes, and Anaerobic Bacteria.**
- Initial Antimicrobial Regimens include **Ertapenem, Piperacillin/Tazobactam, Cefotetan, Ampicillin/Sulbactam, Linezolid**, or **combination of Clindamycin and a Fluoroquinolone.**

- Severe Infections, or Infections that **do not improve after 48 h** of Antibiotic Therapy, require expansion of antimicrobial therapy to treat MRSA (e.g., **Vancomycin**) and Pseudomonas Aeruginosa.
- **If the infection surrounding the ulcer is not improving with IV antibiotics**, **Reassessment of antibiotic coverage** and Reconsideration of the need for **surgical debridement** or **Revascularization** are indicated.
- **With Clinical Improvement**, **Oral antibiotics and local wound care** can be continued on an **outpatient basis with close follow-up**.
- **Peripheral Arterial Bypass Procedures** are often effective in promoting wound healing and decreasing the need for amputation of the ischemic limb.

Management based on IDSA classification of severity of infection

- **Uninfected**
  - Treatment of risk factor and follow up
- **Mild infection**
  - Can be treated with broad spectrum oral antibiotics at OPD with close follow up.
  - Antibiotics include; Cephalosporin, Clindamycin or metronidazole, Amoxicillin/Clavulanate, and Fluoroquinolones
- **Moderate to severe infections**
  - Need hospital admission for IV antibiotics (ceftriaxone or cefotaxime with metronidazole are available in most setups of Ethiopia).
  - Consider anaerobic coverage
  - Modify Antibiotics based on culture result
  - Duration is at least for 4 to 6 weeks (parenteral antibiotics for at least 2 weeks, the rest completed with PO antibiotics)
  - Surgical debridement required for tissue abscess and local gangrene.
  - Those with extensive and life-threatening gangrene may require amputation.

Management based on Wagner Grading

- Grade 0: No Ulcer, Risk Factors Present
  - Education about foot care
- Grade 1: Superficial Ulcer
  - Relief of Pressure
  - Good local wound care
  - Treatment of Infection: PO antibiotics
- Grade 2: Deep Ulcer ± Infection, No Bony Involvement
  - Treat as Grade 1, if no Improvement → Admit and extensive debridement
- Grade 3: Infected Ulcer with Bony Involvement
  - Admit to Hospital
  - Relief pressure
  - Local wound care

    - Debridement
    - Initiate Antibiotics: Triple antibiotics
- Grade 4: Localized Gangrene
    - Treat Like Grade 3
    - Improve Circulation
    - Diffuse Arterial Disease May Require Major Amputation
- Grade 5: Gangrene of Whole Foot
    - Urgent Hospital Admission
    - Antibiotics
    - Surgical consultation and Amputation

10.2 DKA and HHS

Clinical features and how to write hx of DKA patient

History

DKA patients usually present with **LOC** or **severe abdominal pain and vomiting that mimics acute abdomen.**

- ✓ If a known DM patient ask those questions mentioned under Diabetic foot ulcer
- **Poly symptoms (3P)**
    - **Poly urea** → Write in terms of Day to Night ratio (e.g. poly urea of 8:6 day to night ratio).
        - The 24-hour urine voided by a healthy adult range from 600 to 2000ml
        - **Polyuria considered when there is** consistent elimination of an abnormally large volume of urine, **> 2000ml/24h**
    - **Polydipsia** → ask How much litre of water he/she drinks per day
    - **Polyphagia** → less common smx than Polydipsia and Polyuria
- **Per umbilical abdominal pain** that mimic acute abdomen
- **Vomiting**, Nausea, Anorexia, weakness
- **LOC**
- Symptoms of infection or other precipitants

Precipitant factors for DKA & HHS → 4I's

- Infection (30-50%) → pneumonia, UTI, Gastroenteritis, malaria, Sepsis…
- Inadequate **Insulin** Rx (20-40%) → due to non-compliance (in our set up) or insulin pump failure (in westerns set up)

- Infarction → MI, cerebral infarction, mesenteric infarction (intestinal or mesenteric thrombosis), peripheral infarction, (N.B MI is silent in DM)
- In addition (Others)
    - CVA
    - SDH
    - Acute PE
    - Intestinal obstruction
    - Acute pancreatitis
    - Severe burn, hyper/hypothermia
    - Endocrine disorders→ thyrotoxicosis, Cushing sxx, acromegaly
    - Drugs→ cocaine, olanzapine, lithium, alcohol
    - Pregnancy

N.B

- DKA can occur
    - In Previously undiagnosed and untreated DM
    - Due to Interruption of Rx
    - 2ry to Stress of inter current illness (i.e. precipitant factors)

Complication of DKA

DKA, if not detected and treated early it may end up with complications like;

- **Cerebral edema** → ranging from LOC up to death
- **Aspiration** – patients with altered state of consciousness and vomiting are at increased risk for aspiration
- **Pulmonary edema**
- **Electrolyte and acid base disturbance** → like hypokalemia
- Cardiac **arrhythmia** – Cardiac arrhythmias may be seen with either hypokalemia or hyperkalemia. In addition, asystole can be caused by inappropriate administration of IV potassium during treatment of hypokalemia.
- **Venous thrombosis and DVT** → may in part be due to a prothrombotic state associated with DKA
- Pancreatic enzyme elevations

Sample history

Chief compliant

Abdominal pain and vomiting of 03 days duration

HPI

A known DM patient for the past 4 years taking insulin injection 20 units in the morning and 10 units at night. With alternative injection sites between his upper arms, thighs and periumbilical area. Stores his insulin in wet sand bag. He was adherent for his medication with regular follow up every 2 - 3 months in UOG hospital.

Currently presented with severe, crampy, localized, Peri umbilical abdominal pain and non-blood tingled, non-projectile, non-foul-smelling Vomiting of ingested matter 3 - 4 times per day of 03 days duration, but no change in mentation.

A week before the onset of these symptoms, he was experiencing polyuria of 6 - 8 times during night and 9 -10 times during daytime with increased feeling of thirst for which he drinks 3 - 5 liters of water per day but no polyphagia. But he didn’t seek treatment because he assumes it as it was similar to the symptoms he experienced during initial diagnosis and planning to tell his doctor during follow up.

- *Ask those +ve and -ve statements listed on the sample hx of a DM patient above.*
- Two weeks before admission, he also experienced dry cough occurring mostly at night which was exacerbated by deep breathing associated with chest pain and high grade intermittent fever where he visited a private clinic and he was given a tablet to be taken 3 times per day for 7 days and another tablet to be taken once daily for 3 days and he was improved. (pneumonia is precipitant factor for this patient)
- No hx of burning sensation during urination, flank pain or hematuria (UTI as precipitant)
- No hx of diarrhea, nausea or vomiting *(gastroenteritis as precipitant)*
- He is not from malaria endemic area and no travel hx to malaria endemic area *(malaria as precipitant)*
- No hx chest pain, dyspnea or family hx of sudden cardiac death *(MI as precipitant factor)*
- No hx of headache, body weakness or head trauma *(stroke, SDH as precipitant factor)*

Physical examination (pertinent findings)

- ✓ **Assess all pertinent findings listed above for DM pt’**

1 GA

- ✓ ASL→ from abdominal pain
- ✓ LOC (comma)
- ✓ Respiratory distress
- ✓ Fruity breath from Acetone, sweaty and sickly smell

2 Vital signs

- ✓ Hypotension or OHT → from dehydration
- ✓ Tachycardia (fast and weak pulse)
- ✓ Hypothermia
- ✓ Kussmauls breathing (deep, fast and laboured breathing followed by apnea)

3 HEENT

- ✓ Dehydration signs (Dry mucous membrane, sunkening of eyeball)

4 LGS

5 RS

6 CVS

- ✓ Decreased JVP

7 Abdominal examination

- ✓ Abdominal tenderness
- ✓ Reduced skin turgor(dehydration)

8 GUS

9 MSS

10 IS

- ✓ Dry skin

11. NS

- ✓ Mental confusion up to coma (lethargy, obtunded) from cerebral edema

N.B Dehydration signs are common in DKA (more common in HHS than DKA)

- ✓ Sunkening of the eye ball, Dry buccal mucosa
- ✓ Slow skin turgor in the abdomen
- ✓ Eagerness to drink
- ✓ Decreased level of consciousness

DDX of DKA

For poly symptoms refer DDX for DM above

For LOC (coma)

1. HHS
2. Alcoholic ketoacidosis
3. Starvation ketoacidosis
4. Lactic acidosis
5. CKD
6. Drugs → salicyclates, methanol, ethylene glycol
7. For more refer on NS examination /coma/ (click here → 1.4.5 Coma)

IX

1. Blood sugar level → hyperglycaemia (usually >300mg/dl)
2. U/A→ what do you expect from U/A

   a. Glucosuria (> 3+)
   b. Ketonuria (> 2+) → N.B ketonuria is usually +ve in DKA and poorly correlates with ketonemia
   c. UTI
3. CBC → ketonemia, leukocytosis from infection
4. RFT → BUN/creatinine ratio → azotemia
5. Serum electrolyte → wide Anion gap, hyponatremia/hyperkalaemia
6. Calculate plasma osmolality → normal value is **300-320** mosmol/kg

$$\textbf{plasma osmolality} = 2Na + \frac{Glucose}{18} + \frac{BUN}{2.8} \rightarrow (+\frac{Ethanol}{3.7} if\ pt\ ingest\ ethanol)$$

7. Search for precipitant
   a. CXR→ pneumonia
   b. Urine culture → UTI
   c. Blood film → malaria
   d. Echo, ECG, Cardiac markers → MI
   e. CT, carotid Doppler → CVA, SDH
8. Other IX for DM→ refer DM

Discussion

- Diabetic ketoacidosis (DKA) is a condition in which there is a severe deficiency of insulin resulting in very high blood glucose.
- Fat is broken down as an alternative source of energy with ketones/ketoacids as a by-product.
- This state of severe hyperglycaemia and ketone body production results in severe metabolic, fluid and electrolyte abnormalities.
- DKA often occurs in type 1 diabetes patients but may also occur in type 2 diabetes.
- Hyperglycaemic hyperosmolar state (HHS) is a hyperglycaemic emergency that occurs in type 2 DM due to relative insulin deficiency and inadequate fluid intake.
- Apart from acidosis the manifestations, risk factors and management of HHS is similar to DKA
- N.B ketone bodies include
    - ☛ Beta hydroxy butrate
    - ☛ Aceto acetate
    - ☛ acetone

Table; Diagnostic criteria for DKA and HHS

Parameters	DKA			HHS
	Mild	Moderate	Severe	
Clinical	Oriented, **alert** but fatigued	Oriented but **sleepy,** arousable,	Kussmaul or depressed respirations;	**Stupor/coma**

		Kussmaul respirations;	**sleepy to depressed sensorium to coma**	
RBS (mg/dl)	>250			**> 600**
Arterial PH	7.25 - 7.30	7 - 7.24	<7	>7.30
Serum bicarbonate (mEq/l)	15 — 18	10 to <15	<10	> 15
Anion gap (Na^+ - (cl + HCO_3))	>10	>12	>12	Variable
Osmolality (Mosm/kg)	Variable			>320
Urine ketone	Positive			Small
Serum ketone	Positive			Small

Difference between DKA and HHS

DKA	HHS
- RBS > 250 mg/dl - Common in type 1 DM - Present with severe abdominal pain, vomiting or LOC - Strong hx of poly smx's and weight loss - Urine and serum ketone highly rise - 5% mortality - Have 3 cardinal features ☛ Hyperglycaemia ☛ Acidosis ☛ ketosis - Variable osmolality	- RBS > 600 mg/dl - Common in type 2 DM - Present with profound dehydration, hypotension, tachycardia or LOC - Weak hx of polyuria or weight loss - Urine and serum ketone normal or slightly rise - 15% mortality - **Severe osmotic diuresis,** insulin sufficient to suppress lipolysis - Osmolality > 320

Management of DKA

Principles of mgt

- ABCD of life
- **Resuscitation** by expanding intravascular volume (fluid replacement therapy)
- **Potassium** replacement therapy
- **Insulin** therapy
- Treat complications
- Treat precipitating factors
- Monitoring

Non-Pharmacologic

- Mild DKA → in a ward patient can be very closely observed
- Moderate to severe DKA → Admit to ICU
- Closely monitor fluid input and urine output

Pharmacologic

1. **Replace fluids:** Individualize fluid needs based on the patient hydration status; the following is a guide to severely dehydrated patients.
   - **Initial fluid**
     - ✓ **1000ml NS over the first one hour.** (for pediatrics, 10 ml/kg over 1hour, and may be repeated if necessary. In the rare patient with DKA who presents in shock, give isotonic saline in 20 ml/kg bolus infused as quickly as possible)
     - ✓ Reassess for hydration status: if still severely dehydrated, give another 1000ml NS over the next 01 hour.
   - **Subsequent fluid**
     - ✓ Depends on the hydration status and urine output of the patient.
     - ✓ On average give about 250 mL/hour (1000ml over 04 hour) in the first 24 hours or until patient is able to take enough oral fluids.
     - ✓ Reassess the patient hydration status to decide subsequent Iv fluid needs.
     - ✓ For pediatrics, calculate the fluid required.

       fluid required =

       $$\frac{\text{Maintenance fluid (48 hours)} + \text{Deficit fluid (85 X Wt)} - \text{Minus Bolus fluid (which you gave above)}}{48hrs}$$

Table; Calculation of maintenance fluid	
Weight	Amount of IV fluid for maintenance
The first 10 KG	100ml/kg /24hour
From 10 kg to 20 kg	1000ml + 50ml/kg (for kg above 10 kg) eg 13 kg = 1000ml+3x50ml=1150
Above 20 kg	1500ml+ 20ml/kg above the 20kg eg 22k child: 1500ml+20mlX 2kg =1540ml

   - **Changing fluid**
     - ✓ Change the NS to DNS (5%DW9D) when plasma glucose reaches 250 mg/dl in DKA and 300mg/dl in HHS. (i.e. If blood glucose drops below 250mg/dl Change fluid to 5% DW in ½ NS (half of the fluid NS and half DW)). **This will continue until urine is ketone free**.
     - ✓ As long as the patient remains acidotic, insulin administration should never be stopped. if instead drop in the blood sugar need to be addressed by adding or increasing glucose administration in the IV fluid;
     - ✓ **Maintain the blood glucose between 150 and 250 mg per dL.**
   - Fluid is used to treat
     - ✓ DHN
     - ✓ Hyperglycaemia (since fluid induce glucosuria)
     - ✓ Metabolic acidosis
   - HHS requires more fluid.
   - Assess hydration status, BP and urine output frequently.
   - In patients with impaired kidney function and cardiac disease more frequent monitoring must be performed to avoid iatrogenic fluid overload.

2. **Administer short-acting insulin**
    - Don't start Insulin in the first hour of management! It should be started after an hour of fluid resuscitation in order to steadily decrease the acidosis and it increases complication like shock, hypokalemia and cerebral edema
    - **Regular Insulin**
        - ✓ 10 units IV and 10 units IM, stat, (N.B. 10 IU is considering 70 kg Average adult so, use 0.1 IU/kg bolus) then
        - ✓ If there is perfuser: 0.1units/kg/hr by continuous IV infusion. (dilute 50 units regular insulin in 50 ml NS to make 1 Iu=1ml soln. Run 0.1IU /kg /hour with a syringe per fuser)
        - ✓ If there is no perfuser: 5 units, IV, every 1 hour[13]. **IV regular insulin should be continued** until the acidosis resolves and the patient is metabolically stable (i.e. **until the patient is out of DKA**). Then change to transition phase dose (look at below).
    - **Goal**[14]
        - ✓ Reduce serum glucose by 50 to 70 mg/dl in the 2-3 hours
        - ✓ If the drop is <50mg/dl in 2-3 hours, double the regular insulin.
        - ✓ If the drop is faster, reduce the dose by half for continuous infusion and give the IV insulin every 2 hour. i.e. If RBS is < 250mg/dl reduce the infusion by half (from 0.1units/kg/hr to 0.05units/kg/hr)
            - More rapid correction of the serum glucose can precipitate the development of cerebral edema.
        - ✓ Determine RBS every one hr, urine ketone and glucose every 2hr

3. **Potassium**
    - All patients with DKA have potassium depletion irrespective of the serum K^+ level.
    - N.B. total K^+ level is low in DKA, but serum K^+ level can be normal, high or low
        - ✓ If the initial serum K^+ is <3.3 mmol/l, do not administer insulin until the K^+ is corrected.
        - ✓ If the initial serum K^+ is > 5.3 mmol/l, do not supplement KCl until the level reaches < 5.3.
        - ✓ If K^+ determination is not possible delay initiation of K^+ replacement until there is a reasonable urine put (>50 ml/hr)
    - Add intravenous KCl in the IV fluids (20-40 meq of KCl in each bag of NS) **N.B. 1 vail of Kcl = 20 meq**
        - ✓ Add 40 meq of Kcl in IV fluid when serum K^+ is within 3.4 - 4.5 mmol/l

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[13] IV administration of regular insulin is usually preferred because it ensures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. DKA can also be treated with SC short-acting insulin analogues.

[14] Acidosis and ketosis resolve more slowly than hyperglycemia. As ketoacidosis improves, β-hydroxybutyrate is converted to acetoacetate. Ketone body levels may appear to increase if measured by laboratory assays that use the nitroprusside reaction, which only detects acetoacetate and acetone.

    - ✓ Add 20 meq of Kcl in IV fluid when serum K^+ is within 4.6 - 5.0 mmol/l
    - ✓ If less than 3 mmol/L after the initial bolus: upto K+ of ≥ 60 mEq/ L may be necessary.
  - The serum potassium should be maintained between 4.0 and 5.0 mmol/l
  - If possible, determine K^+ level every 6hr
  - The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/h. and If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced (decrease by half dose)

4. **Treat complication of DKA mgt**
    - ❖ Hypoglycaemia
    - ❖ Hypokalemia
    - ❖ Non cardiogenic pulmonary edema
    - ❖ Cerebral edema → manifest with decreased level of consciousness (lethargy, obtunded, coma), headache. It is fatal cxn

5. **Precipitant identification and treatment**
    - Noncompliance, infection, trauma, infarction. Initiate appropriate workup for precipitating event (cultures, CXR, ECG)

6. **Follow up of response**
    - Blood glucose every **1** - 2hrs
    - Urine ketones and glucose every **2** - 4hr
    - Electrolytes (especially K^+) every 6 hr for first 24 h.

7. **Continuation of treatment**
    - The above treatment should continue until the patient is stable, clinically acidosis improves, and patient is able to take oral feeding.
    - The urine ketone might still be positive, as it usually lags behind the improvement of acidosis.

8. **Transition**
    - Once the patient is able to take oral feeding and clinically the acidosis improved (i.e out of DKA).
        - ✓ **Reduce regular insulin**: 2-3 units hourly (5 units every 2 hour) or for continuous infusion by 0.05/kg per hour
        - ✓ **Overlap regular insulin infusion** with subcutaneous **(SC) NPH** insulin **for 2-3 hours** to avoid rebound hyperglycemia. And this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay.[15]

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[15] It is crucial to continue the insulin infusion until adequate insulin levels are achieved by administering Sc NPH. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse.

  - In the other way, Because of the short half-life of IV regular insulin, it is necessary to administer long-acting insulin (NPH) prior to discontinuation of the insulin infusion (2—3 h before the infusion is stopped) to avoid a period of insulin deficiency.
  - **NPH insulin dosing**
    - If previously on insulin: start the pre DKA or pre-HHS dose
    - If Insulin naïve: 80% of the 24-hour requirement or 0.5 to 0.8 IU/kg/day /some says 0.5 to 1 IU/kg/day/ (divided in to basal and bolus)
- ✓ **After 2-**3 hr of overlap
  - Discontinue Regular insulin infusion
  - Continue Sc NPH as morning and evening dose and
  - Start sliding scale method of Regular insulin IV dose (correction dose mgt) → Look at below

When do you say patient is out of DKA (Resolution of DKA)?

- ❖ **Recovery of clinical condition** → we use in our set up
  - ☛ Recovery to mental Alertness
  - ☛ Able to take PO feeding
  - ☛ Norma respiration (No kussmauls breathing, desaturation or SOB
  - ☛ If precipitant treated
- ❖ **Blood glucose < 250 mg/dl** → we use in our set up
- ❖ Serum ketone -ve
- ❖ Serum bicarbonate >18
- ❖ PH > 7.3
- ❖ Anoin gap <12
- ❖ Osmolarity <320 mosmol/kg

} not available in our set up

MANAGEMENT OF DIABETES IN A HOSPITALIZED PATIENT

- ➢ Glycemic goals for hospitalized patients: 140 - 180 mg/dL
- ➢ The use of **"sliding scale,"** Regular insulin alone, where no insulin is given unless the blood glucose is elevated, is inadequate for inpatient glucose management and should not be used.
- ➢ Regular insulin dose should include corrective or supplemental insulin based on the patient's insulin sensitivity and the blood glucose. For example, **if the patient is thin (and likely insulin-sensitive),** a corrective insulin supplement might be **1 unit for each 50 mg/dL over the glucose target (i.e. > 180mg/dl).** If the patient is obese and insulin-resistant, then the insulin supplement might be 2 units for each 50 mg/dL over the glucose target.
- ➢ It is critical to individualize the regimen and adjust the basal or "scheduled" insulin dose frequently, based on the corrective insulin required.

Correction dose (Sliding scale)

- Correction dose will be given when the patient is out of DKA / usually pt transferred from ED to ward/
- Measure RBS every 1 hour then give Regular insulin IV push based on the following table

Table; Sliding scale		
RBS (in Mg/dl)	Regular insulin dose (IU), IV route	
	For thin and insulin-sensitive pt	**For obese and insulin-resistant pt**
≤ 180	**Omit**	**omit**
181 — 230	1	2
231 — 280	2	4
281 — 330	3	6
331 — 380	4	8
381 — 430	5	10
431 — 480	6	
481 — 530	7	
531 — 580	8	
581 — 600	9	
>600 (High)	10	

- ☛ In addition to RI, continue subcutaneous NPH insulin dosing that is given at transition phase above.
- ☛ When RBS is in the target range sliding scale will be omitted. After sliding scale, follow RBS q 4hr, then QID and consider discharge to Diabetic clinic with short appointment after diabetic education.

Insulin dose during discharge

- NPH dose is the same as given at transition phase which can vary based on RBS control.
- For Regular insulin dosage, calculate the total amount of regular insulin given as correction dose over 24hrs → then give 2/3rd of the total dose in the morning and 1/3rd in the evening
- Then from the total dose of insulin requirement the content should be mixed with 2/3rd of NPH and 1/3rd of regular for both morning and night doses via subcutaneous route
- e.g. if total amount of regular insulin given over 24hr as correction dose is 12 IU of regular insulin, and NPH was 24 IU. The total summation (mixed) will become 36 IU → 2/3rd of 36 IU = 24 IU, 1/3rd of 36 IU = 12 IU, so give 24 IU (16 IU of NPH and 8 IU of RI) in the morning and 12 IU (8 IU NPH and 4 IU RI) in the evening

- Some experts prefer the evening dose to be 1:1 ratio of NPH and regular insulin. For the above example; 6 IU of NPH and 6 IU of RI as evening dose.

DKA follow up sheet

Date	Time	BP	PR	RR	T^0	Mentation	RBS/hr	Urine glucose/ 2hrs	Urine ketone /2hrs	Insulin dose (IU, IV)	input	Out put	sign

Assume you are in a primary hospital where chemistry machine is not available, so you can order like these

- Secure double IV line
- Keep NPO
- Resuscitate with 2 – 3 bags of NS over 2hr's
- Then give Regular insulin 10 IU, IM & 10 IU, IV Followed by 5 IU, IV, Q1hr
- Change fluid to DNS if RBS is < 250mg/dl (see transition period part above)
- Determine RBS Q1hr & Urine ketone Q 4hr's
- Follow with DKA follow up sheet

➢ N.B for DKA in Type II DM patients

✓ Oral glucose lowering agents should be discontinued upon admission and are not useful in regulating the plasma glucose in clinical situations where the insulin requirements and glucose intake are changing rapidly. Moreover, these oral agents may be dangerous if the patient is fasting (e.g., hypoglycemia with sulfonylureas)

✓ Once clinically stable, oral glucose-lowering agents may be resumed in anticipation of discharge.

✓ Ketosis is one of the indications to start insulin alone or in combination with oral hypoglycemic agents (look at Type II DM mgt above)

10.3 Hypoglycaemia

- Hypoglycemia is a blood sugar level low enough to cause symptoms and signs. A value **<70mg/dl in diabetes** and **<55mg/dl in non-diabetic** patient defines hypoglycemia.

- Some patients might be symptomatic at levels>70mg/dl and some might not develop symptoms at level <70mg/dl
- It is a clinical syndrome in which low serum (or plasma) glucose concentrations leads to symptoms of sympathoadrenal activation and neuroglycopenia.
- It can cause significant morbidity and may be lethal if not promptly recognized and managed.
- It is a common complication of glucose lowering therapy in diabetes (cmnly from Sulfonylureas and insulin).
- The elderly, patients with impaired kidney function and multiple comorbidities are at higher risk of hypoglycemia.
- **Pseudohypoglycemia** → the person with diabetes reports typical smx's of hypoglycemia but RBS >70 mg/dl. These patients commonly have chronically high blood sugar.

- **Whipple's triad** → useful for the Dx of hypoglycemia in general.
    1. Symptoms and signs of hypoglycemia
    2. Documented low blood glucose level (<70mg/dl in diabetes and <55mg/dl in non-diabetic patient) measured with a precise method (not a glucometer)
    3. Relief of symptoms up on correction of the low blood glucose.

- **Hypoglycemia unawareness**-absent symptoms in spite of having low blood glucose levels (usually related to autonomic diabetic neuropathy)

Clinical features

- The symptoms of hypoglycemia are classified in to autonomic and neuroglycopenic

Autonomic		**Neuroglycopenic (brain glucose deprivation)**
Adrenergic	**Cholinergic**	
Palpitation and tachycardia Tremor Anxiety Nausea	Hunger Sweating sensation of warmth Paresthesia (Tingling)	Difficulty concentrating Difficulty in speaking Abnormal behavior Loss of memory Blurred vision Incoordination Confusion LOC Seizure Fatigue Dizziness Headache Drowsiness
Mnemonic for C/F of hypoglycemia → "He IS TIRED" ☛ Headache		

- Irritable
- Sweating
- Tachycardia
- Incoordination
- Restless
- Excessive hunger
- Dizziness

Major causes of hypoglycemia:

- In DM pt
  - ✓ Insulin and sulfonylureas excess dose or previous doses with unaccustomed exercise
  - ✓ omission of meals.
  - ✓ Development of CKD, AKI, and sepsis.
- In non-diabetic patients with critical illnesses
  - ✓ Hepatic or renal failure
  - ✓ Adrenal insufficiency
  - ✓ Sepsis
  - ✓ Malaria.
- In Seemingly normal patients
  - ✓ Endogenous hyperinsulinemia
  - ✓ Accidental or surreptitious use sulfonylureas or insulin.

NB: Hypoglycemia caused by sulfonylureas can be prolonged for several days. Hence these patients should not be discharged with emergency room correction of hypoglycemia alone

Investigations and diagnosis

Diagnosis

- ➢ Hypoglycemia in diabetes diagnosed with either of the following
  - ○ RBS <70mg/dl in diabetes and <55mg/dl in non-diabetic patient.
  - ○ Presence of symptoms which improve with treatment
- ➢ Classification of diabetes associated hypoglycemia based on severity

Level (severity)	Characteristics
1 (mild)	RBS = 54-70 mg/dl
2 (moderate)	RBS <54 mg/dl
3 (severe)	**Altered mentation** and/or physical status **requiring assistance for treatment** of hypoglycemia

Investigations

- ✓ Glycemia related: FBS, postprandial blood sugar and HbA1c

- ✓ Creatinine and urea

Management of hypoglycaemia

Non-pharmacologic

- ➢ The main stay of management of level 1-2 (mild to moderate) and level-3 (severe) hypoglycemia with preserved consciousness taking or providing glucose rich food/drinks(sweets).
    - o Pure glucose is preferred but any carbohydrate rich food can be used
- ✓ Give 04 teas spoon of sugar diluted in water
- ✓ Monitor blood sugar every 20-30 minutes
- ✓ If no improvement repeat the above
- ✓ Once blood sugar improves, the patient must take a meal or snack
    - o Alternatives: regular soft drinks
- ✓ 200ml of Mirinda® or Cola® contains about 20gram sugar can replace the above.
    - o Avoid protein rich foods as they increase insulin response
- ➢ For hypoglycemia unawareness: a 2-3 weeks period of avoiding hypoglycemia through frequent self-monitoring of blood glucose and keeping the blood glucose at higher levels may restore awareness.

Pharmacologic

- ➢ In patients who present to health facilities with decreased level of consciousness from severe hypoglycaemia
    - o 40% Dextrose/**D40/**
        - ✓ Give **03 vials** (60ml = 24g), IV, fast
        - ✓ Monitor blood sugar every 20-30 minutes
        - ✓ If blood sugar is <70mg/dl, give another 03 vials of 40% dextrose and start 5-10% dextrose (i.e. **D10** or D5) **infusion**. Continue to monitor blood sugar every 20-30 minutes.
        - ✓ In some references; it says, 40-60ml of D40 over 1 to 3 minutes through a large vein, followed by D10%
        - ✓ **Glucose** IV, 500ml, 4 hourly until the patient is able to eat normally.
        - ✓ **Glucagon** SC/IM 1mg in adults particularly in type I DM patients.
        - ✓ When the patient can take orally give regular meal or snack.

N.B 1 vial of D40 = 20ml = 8g. How?
40 % of 20ml = $\frac{40}{100}\,x\,20ml = 8ml = 8g$

Prevention of hypoglycemia in diabetics

- ✓ Self-monitoring of blood sugar
- ✓ Patient, family/care giver education

  - A standardized education on rigorous avoidance of hypoglycemia
  - On conditions which increase the risk of hypoglycemia
    - ✓ Fasting or delayed meals
    - ✓ Consumption of alcohol
    - ✓ Intense exercise
  - Symptoms of hypoglycemia and possibility of hypoglycemia unawareness
  - Treatment of hypoglycemia at earliest warning symptoms or at <70mg/dl
  - Adjusting glycemic targets to higher levels, if hypoglycemia is recurrent
  - Reporting episodes of hypoglycemia to physician

Chapter 11; AKI/Acute kidney injury/ and CKD/ Chronic kidney disease (የኩላሊት በሽታ)

Dr. Mulualem. G, Dr. Robel. D

Clinical features and how to write hx of CKD patient

History

- Pt's may present with
    - **Generalized body swelling (GBS)**
    - Vomiting
    - Decreased urine out put
- GBS
- Site → swelling over the face and around the eyes (i.e. facial puffiness)
- Duration → long standing (e.g. 4 months duration)
- Progression… e.g. progress to the legs with in ''X'' days and finally to the whole body with in ''Y'' days
- Diurnal variation → more prominent early in the morning/while s/he awakes from sleep.
- How the pt noticed the swelling
- Painful or not → Mostly painless

N.B body swelling

- **In cardic pt. →start from leg and goes upward**
- **In renal disease → begin from face (morning facial puffines)**
- **In liver disease → start with abdominal distension which may progress to GBS**

- SOB → exertional dyspnoea
- Haematuria, flank pain (stabbing type of pain)
- Change in urine amount (oliguria, anuria → estimate the amount in terms of ml per day) or in the other way frequency, urgency, dysuria…
    - After long period of these symptoms pt may present with **vomiting**
- Fever
    - High grade
    - Intermittent
    - Associated with night sweat, chills/rigor
- Weight loss

Risk factors

- See etiologies of AKI from Discussion part below
- HTN → HTN and CKD are interchangeable cause of one another
- DM
- Dyslipidaemia,
- Sedentary life style
- Old age
- Auto immune disease (e.g. glomerulonephritis)
- Family history → RF for PCKD
- Previous AKI
- Drugs
    - Immunosuppressive drugs
    - Nephrotoxic drugs are reversible factor for renal failure (NSAID's, ACE-I/ARB, cyclosporin cause AKI 2ry to acute tubular necrosis → CKD)
- African ancestors
- Evidence of kidney damage
    - Proteinuria
    - Abnormal urinary sediment (casts)
    - Structural urinary tract abnormality
- Aetiologies → top 5 aetiologies for CKD
    1. Diabetic nephropathy → cmn cause of CKD in north America and Europe
    2. Glomerulonephritis → cmn cause of CKD in developing countries (especially post streptococcal GN) like in our setup (Ethiopia)
    3. Hypertensive nephropathy
    4. PCKD
    5. Cystic and tubule interstitial nephropathy

Complication of AKI

- Uremia and complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding)
- Hypervolemia and hypovolemia
- Electrolyte disturbance
    - Hyponatremia
    - Hyperkalemia
    - Hyperphosphatemia and Hypocalcemia
- Metabolic acidosis
- Hematologic complications
    - anemia
    - bleeding
- Infections
    - Infections are a common precipitant of AKI and also a dreaded complication of AKI.
- cardiac complications of AKI
    - arrhythmias

  - pericarditis
  - pericardial effusion.
  - In addition, volume overload and uremia may lead to cardiac injury and impaired cardiac function.
- Malnutrition

Complication of CKD

- Fluid, electrolyte and acid base disturbance
- Disorders of calcium and phosphate metabolism
  - Bone fracture, bone pain
- Cardiac and vascular calcification
  - CAD/coronary arterial disease/
  - CVD/cerebrovascular disease like stroke/
  - PAD/peripheral arterial disease/)
- HTN and Left Ventricular Hypertrophy, DCMP, pericarditis, Heart Failure
- Anaemia → Causes of Anemia in CKD include
  - Relative deficiency of erythropoietin
  - Diminished red blood cell survival
  - Bleeding diathesis
  - IDA (Iron deficiency due to poor dietary absorption and GI blood loss)
  - Hyperparathyroidism/bone marrow fibrosis
  - Anemia of chronic disease (Chronic inflammation
  - Folate or vitamin B 12 deficiency
  - Hemoglobinopathy
  - Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs
- *Uremic fetor*
  - a urine-like odor on the breath, derives from the breakdown of urea to ammonia in saliva and is often associated with an unpleasant metallic taste (dysgeusia
- Gastritis, PUD
- CNS, ANS and PNS neuropathy
- Uremic encephalopathy
- Impaired Glucose metabolism
  - Hyperglycaemia and DM treatment CXN → because of decreased urinary insulin excretion
- Pruritus from uremia

Sample history

Sample hx of a pt’ from Maksegnit with a DX of AKI on CKD. (sample taken from our friend Dr. Natnael Bedilu (GP), which was his round case during our C-I attachment)

Chief compliant

GBS of 2 weeks duration

HPI

This patient was last relatively healthy 2 weeks back, at which time his father noticed swelling around the eyes and face that was more marked early in the morning. Over a period of 3 days the swelling progress to involve the abdomen and the legs then becomes generalized. Concomitantly the patient starts to experience shortness of breath which was felt initially while doing supra ordinary activities like going uphill’s which later worsen over a week to be felt at ordinary activities like going 15minute walk to the school he was attending associated with palpitation but no orthopnea, PND, chest pain or intermittent claudication.

One week before admission, he started to experience a decreased in urine amount of approximately 200 to 250ml per day, bilateral stabbing type of flank pain with no radiation or a known aggravating or relieving factor but no frequency, urgency, pain during micturition or urine color change.

In addition to this the patient was complaining of nausea, loss of appetite and dull aching type of epigastric pain without radiation or any aggravating or relieving factor but no history of vomiting, bowel habit change or weight loss. (ureamic sxx, ESRD, Gastritis and PUD → CXN)

For this compliant he visited local health center at tseda where he was given unspecified white oval tablet to be taken 3X per day prescribed for 10 days but he discontinued the treatment since he was not getting any improvement of the symptoms and he come to our hospital for better investigation and management.

12 years back he had experienced reddish discoloration of urine and generalized body swelling for which he was admitted at UOG hospital where he was told that he was having kidney disease. He was then given unspecified tablets and injectable medications and he was on salt free diet. After 3 weeks of hospital stay, he was discharged with follow up and improved. He was relatively fine until the current admission.

- No hx of DM, HTN or asthma *(DM and HTN cause CKD, DM cause 2ry nephrotic sxx → RF)*
- No hx of drug intake other than those mentioned above *(Drugs like Aminoglycosides, NSAID’s, Metformin are RF for Intrinsic AKI and CKD)*
- No family hx of similar illness *(RF for PCKD)*
- No hx of tinnitus, blurring of vision, light headedness or easy fatigability *(anaemia → CXN)*
- No hx of LOC, confusion, bizarre behaviour, forgetfulness, disturbance of speech, visual disturbance or abnormal body movement *(ureamic encephalopathy → CXN)*
- No hx of nasal/gum bleeding or bleeding from other sites *(hematologic CXN of CKD)*
- He has dyspnoea but no hx of chest pain, orthopnea or PND *(IHD, pericarditis, CHF → CXN of CKD or DDX for GBS)*
- No hx of malar rash, photosensitivity or joint pain *(SLE cause 2ry Nephrotic SXX → DDX)*

- No hx of chronic cough, contact with chronic cougher or previous TB treatment *(TB enteritis, renal TB → DDX)*
- No hx of RUQ abdominal pain, yellowish discoloration of the eye or contact with a jaundiced person *(CLD → DDX)*

Finally, he was admitted to our hospital supported physically by his families

Physical examination (pertinent findings)

1 **GA** → coma (uremic encephalopathy)

2 **Vital signs**

  - HTN → HTN as a cause of CKD or HTN 2ry to CKD
  - OHT (orthostatic hypotension) → hypovolemia 2ry to extra cellular fluid depletion, ANS neuropathy
  - Tachypnoea → from uremic acidosis
  - Tachycardia → extra cellular fluid depletion

3 **HEENT**

- Facial puffiness (part of GBS)
- Pale conjunctiva → anaemia

4 **LGS**

5 **RS**

  - Kussmaul's breathing 2ry to uremic acidosis
- Pleural effusion (part of GBS)

6 **CVS**

- CHF features
- Pericardial friction rub and knock from pericarditis

7 **Abdominal examination**

- Ascites (part of GBS)

8 **GUS**

9 **MSS**

- Oedema (part of GBS)
  - Bone tenderness and fracture
  - PAD features

10 **IS**

11 **NS**

- Stroke features
- Coma

DDX for GBS

1. CKD
2. Nephrotic sxx
3. CHF
4. Constrictive pericarditis
5. CLD
6. Advanced Lymphoma (NHL)
7. Disseminated TB to pleura, Peritoneum…..
8. Hypothyroidism
9. ? PLE

IX

- U/A
    - ✓ Abnormal sediment or cast (hyaline cast, RBC cast, WBC cast) → indicate kidney damage
    - ✓ Proteinuria → indicate kidney damage
    - ✓ Haematuria → glomerulonephritis
    - ✓ cells
- Urine culture and sensitivity → UTI (Pyelonephritis)
- RFT (BUN and Creatinine)
    - ✓ Creatinine clearance (GFR) estimate by Cockcroft-Gault equation in adults and older adolescents (age ≥18 years).

$$\frac{(140 - age)\ x\ \ weight(in\ kg)}{72\ x\ serum\ creatinine\ level\ (mg/dl)}\quad (multiply\ the\ result\ with\ 0.85\ for\ females)$$

    - ✓ BUN/creatinine ratio is normal at 10 to 15:1 in ATN (measured in mg/dL), but is often > 20:1 in prerenal disease
    - ✓ serum creatinine rises progressively and usually at a daily rate > 0.3 to 0.5 mg/dL/day in ATN.

- Serum albumin level (LFT) → hypoalbuminemia from albuminuria
- RBS → diabetic nephropathy
- CBC
    - ✓ Anaemia → NcNc Anaemia
    - ✓ Leucocytosis → UTI (Pyelonephritis)
- Serum electrolyte → fluid and electrolyte disturbance in CKD
    - ✓ Hyperkalaemia
    - ✓ Hyperphosphatemia with hypocalcaemia in chronic renal failure

  - ✓ Hyperuricaemia (raised level of uric acid)
- Abdominal U/S
  - ✓ Estimate renal size (if small kidney → CKD diagnosed possibly, if normal size acute attack rather than chronic)
  - ✓ Obstructive uropathy
- Doppler U/S and MRA of renal artery
- ECG, ECO, CXR → pericarditis (diffuse ST segment elevation), pericardial effusion, CHF, LVH 2ry to HTN
- Immunologic test → SLE, vasculitis
- Renal Biopsy
  - ✓ Reserved only for patients having near normal kidney size when Dx by other Ix modality is difficult
  - ✓ Renal biopsy in AKI
    - **If the cause of AKI is not apparent** based on the clinical context, physical examination, laboratory studies, and radiologic evaluation, kidney biopsy should be considered.
    - The procedure is most often used in AKI when prerenal azotemia, postrenal AKI, and ischemic or nephrotoxic AKI have been deemed unlikely, and other possible diagnoses are being considered such as
      - **Glomerulonephritis**
      - Vasculitis
      - interstitial nephritis
      - myeloma kidney
      - HUS and TTP
      - allograft dysfunction.
    - The kidney biopsy can provide definitive diagnostic and prognostic information about AKI and CKD
    - Kidney biopsy is associated with a risk of bleeding, which can be severe and organ- or life-threatening in patients with thrombocytopenia or coagulopathy.
  - ✓ C/I to renal biopsy
    - — Bilateral small (shrunken) kidney → size < 8.5cm
    - — PCKD
    - — Uncontrolled HTN
    - — active urinary tract infection
    - — UTI / peri nephritis
    - — Bleeding diathesis
    - — Morbid obesity (BMI > 40 Kg/m^2)
    - — Respiratory distress is relative C/I

Discussion

11.1 Acute Kidney Injury (AKI)

- AKI is defined by the impairment of kidney filtration and excretory function over days to weeks, resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys.
- AKI is not a single disease but, rather, a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in serum creatinine (SCr) concentration often associated with a reduction in urine volume.
- AKI is a clinical diagnosis and not a structural one.
- A patient may have AKI with or without injury to the kidney parenchyma.
- AKI can range in severity from asymptomatic and transient changes in laboratory parameters of GFR, to overwhelming and rapidly fatal derangements in effective circulating volume regulation and electrolyte and acid-base composition of the plasma.

Diagnostic Definition of AKI

- **AKI is diagnosed if any one of the following criteria is fulfilled.**
  - Increase in serum creatinine from the baseline by ≥ 0.3mg/dl, which is known to have occurred occur in ≤48 hours. Or
  - Increase in serum creatinine by 50% (1.5-fold) form baseline, which is known or presumed to have occurred within one week (the prior 7 days). Or
  - Urine output <0.5ml/kg/hr for ≥ 6 hours (for an average adult < 200ml/6 hours)

Staging AKI: According to the KDIGO (Kidney Disease Improving Global Outcomes) staging, AKI is staged in to three.

Table. Staging of AKI according to KIDGO*

Stages	Creatinine-based	Urine-out put base
Stage 1	Increase from baseline: 1.5 - 1.9 times (≥50% but <100%) or ≥ 0.3mg/dl	< 0.5 ml/kg/h for 6 - 12 hours
Stage 2	Increase from baseline 2.0 -2.9 times (>100% but < 300%)	Urine output < 0.5 ml/kg/h for ≥ 12 hours
Stage 3	Increase from baseline ➢ 3 times (>300%) OR ➢ An increase to a level >4.0 mg/dl Or ➢ Initiation of renal replacement therapy	➢ <0.3 ml/kg/h for ≥24 hours OR ➢ Anuria for ≥12 hour

* KIDGO is a modification to RIFLE (Risk, Injury, Failure, Loss, ESRD) and AKIN

Distinction between AKI and CKD

- The distinction between AKI and CKD is important for proper diagnosis and treatment.
- The distinction is straightforward when a recent baseline SCr concentration is available, but more difficult in the many instances in which the baseline is unknown.
- In such cases, **clues suggestive of CKD**
  - Radiologic studies (e.g., small, shrunken kidneys with cortical thinning on renal ultrasound, or evidence of renal osteodystrophy)
  - Normocytic anemia in the absence of blood loss
  - Secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia, consistent with CKD.
  - Old records of elevated Cr
  - Symptoms of uremia
- **No set of tests, however, can rule out AKI superimposed on CKD** because AKI is a frequent complication in patients with CKD, further complicating the distinction.
- Serial blood tests showing a continued substantial rise of SCr represents clear evidence of AKI.
- Once the diagnosis of AKI is established, its cause needs to be determined since the elevation of SCr or reduction in urine output can be due to a large number of physiological and pathophysiological processes.

Etiologies and pathophysiology

- **The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia (55%), intrinsic renal parenchymal disease (40%), and postrenal obstruction (5%)**

1. **Prerenal azotemia (55%)**

- Prerenal azotemia (from “azo,” meaning nitrogen, and “-emia,” meaning in the blood) is the most common form of AKI.
- It is the designation for a rise in SCr or BUN concentration due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration.
- The most common clinical conditions associated with prerenal azotemia are
  - ✓ Hypovolemia (any cause e.g. Burns and Acute Pancreatitis, bleeding, profuse vomiting…)
  - ✓ decreased cardiac output (Heart Failure), and
  - ✓ medications that interfere with renal autoregulatory responses such as NSAID and ARB

2. **Intrinsic renal parenchymal disease (40%)**

- **The most common causes of intrinsic AKI are**
  - ✓ **Sepsis**
  - ✓ **Ischemic acute tubular necrosis (ATN)** and
  - ✓ **nephrotoxic ATN** → both endogenous and exogenous. Examples include
    - antibiotics (aminoglycoside *and amphotericin B*, *Vancomycin, penicillins, cephalosporins, quinolones, sulfonamides*, and *rifampin.)*

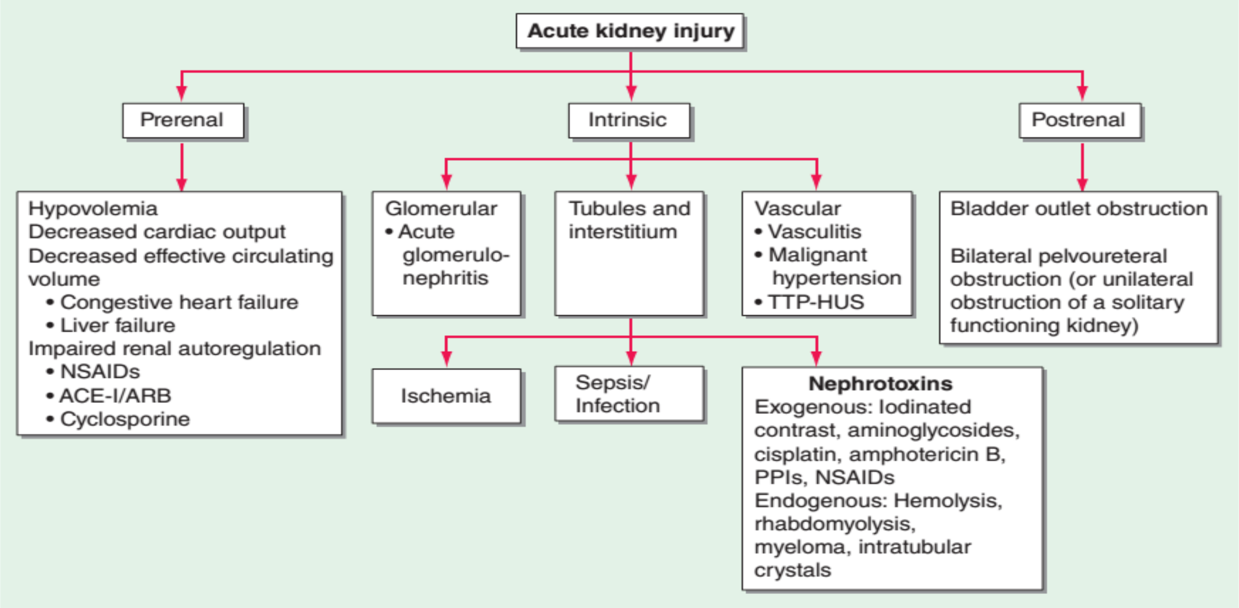
Aminoglycosides are commonest causes of nephrotoxic ATN

- *antiviral drugs (e.g. Acyclovir, Foscarnet, pentamidine, tenofovir*, and *cidofovir)*
- intravenous iodinated contrast
- Chemotherapeutic Agents (e.g. *Cisplatin, carboplatin, bevacizumab,* mitomycin C and gemcitabine)
- Toxic Ingestions (e.g. Ethylene glycol)
- Endogenous Toxins (e,g. myoglobin from Rhabdomyolysis, hemoglobin from massive hemolysis, uric acid, and myeloma light chains.)

- ➢ In many cases, prerenal azotemia advances to tubular injury classically termed “acute tubular necrosis
- ➢ other less common causes of intrinsic AKI include
  - ✓ acute glomerulonephritis
  - ✓ acute interstitial nephritis

3. postrenal obstruction (5%)

- Postrenal AKI occurs when the normally unidirectional flow of urine is acutely blocked either partially or totally, leading to increased retrograde hydrostatic pressure and interference with glomerular filtration
- For AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr.
- Unilateral obstruction may cause AKI in the setting of significant underlying CKD or, in rare cases, from reflex vasospasm of the contralateral kidney.
- Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra
- Causes of obstruction include
  - Bladder neck obstruction is a common cause of postrenal AKI
    - **BOO (Bladder outlet obstruction)**
    - **Prostate cancer**
    - **Neurogenic bladder**, or
    - therapy with anticholinergic drugs.
  - Obstructed Foley catheters (if not recognized and relieved.)
  - **Urethral strictures**
  - bilateral ureteral obstruction
  - Stones, blood clots, external compression, tumor, retroperitoneal fibrosis


Acute kidney injury
Prerenal
Intrinsic
Postrenal
Hypovolemia
Decreased cardiac output
Decreased effective circulating volume
• Congestive heart failure
• Liver failure
Impaired renal autoregulation
• NSAIDs
• ACE-I/ARB
• Cyclosporine
Glomerular
• Acute glomerulo-nephritis
Tubules and interstitium
Vascular
• Vasculitis
• Malignant hypertension
• TTP-HUS
Bladder outlet obstruction
Bilateral pelvoureteral obstruction (or unilateral obstruction of a solitary functioning kidney)
Ischemia
Sepsis/ Infection
Nephrotoxins
Exogenous: Iodinated contrast, aminoglycosides, cisplatin, amphotericin B, PPIs, NSAIDs
Endogenous: Hemolysis, rhabdomyolysis, myeloma, intratubular crystals

Figure; Classification of the major causes of acute kidney injury.
ACE-I, angiotensin-converting enzyme inhibitor-I; ARB, angiotensin receptor blocker; TTP-HUS, thrombotic thrombocytopenic purpura—hemolytic-uremic syndrome.

- The cause of AKI in a single patient can be multiple (multifactorial). This particularly true in critically sick hospitalized patients.
- Whenever a diagnosis of AKI is made, the specific etiology/etiologies should be carefully searched.
- AKI is a common problem clinical problem; it is much more common in hospitalized patients than in the community.
- The common causes of dialysis requiring AKI in Ethiopia used to be severe malaria and septic abortion but recently there is a significant shift in the etiology. Hypovolemia with or without sepsis, glomerulonephritis, and obstetric causes (mainly driven by pre-eclampsia) are the leading causes.
- The elderly, diabetics, patients with underlying CKD, patients with heart failure or liver disease are at high risk of developing AKI.

Clinical features

- The clinical features of AKI are **dominated by those of the underlying cause** unless the AKI is severe.

Symptoms

- Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria causing polyuria, and several medications including diuretics, NSAIDs, ACE inhibitors, and ARBs
- A reduction in urine output (oliguria, defined as <400 mL/24 h) usually denotes more severe AKI (i.e., lower GFR) than when urine output is preserved.
- Red or brown urine may be seen with or without gross hematuria
- Fatigue
- Body swelling
- Shortness of breath
- Poor appetite, nausea and vomiting
- Hiccups
- Bleeding, mucocutaneous

- Symptoms of the underlying cause: e.g. tea/cola colored urine in glomerulonephritis, fever in sepsis/malaria

Signs

- Orthostatic hypotension, tachycardia, reduced JVP, decreased skin turgor, and dry mucous membranes are often present in prerenal azotemia.
- Peripheral edema
- Signs of pulmonary congestion: bilateral lower lung zone crackles
- Signs of pleural effusion or ascites
- Change in mental status/flapping tremor/seizure
- Signs of pericarditis or pericardial effusion
- Signs of the underlying disease: e.g. Cutaneous and joint manifestations in SLE with glomerulonephritis, low BP and signs of dehydration in patients with pre-renal azotemia or ischemic ATN

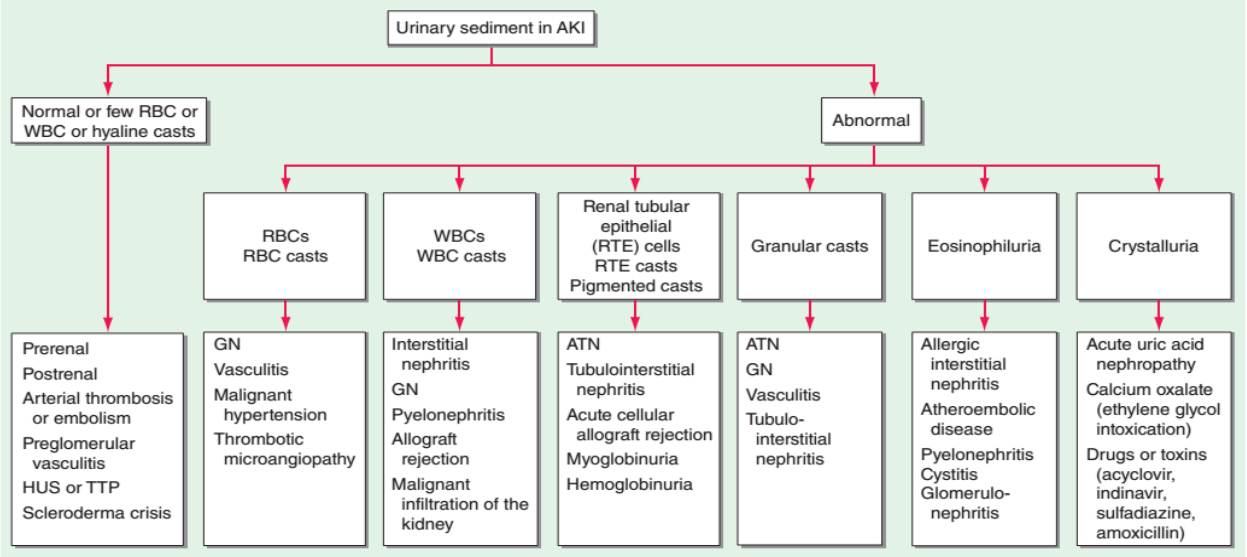
Investigations and diagnosis

Diagnosis

- The diagnosis of AKI is made based on serum creatinine and/or urine output criteria mentioned above. See the diagnostic and staging criteria above.
- Differentiating AKI from chronic kidney disease (CKD) is very important, although it might not always be straight forward.
- The presence of a previous creatinine determination helps in differentiating AKI from CKD.
- Bilateral small sized kidneys (<9cm longitudinally) indicate CKD; however, not all patients with CKD have small size kidneys.

Investigations

- Serum urea and creatinine
- Urinalysis


Urinary sediment in AKI
Normal or few RBC or WBC or hyaline casts
Abnormal
RBCs RBC casts
WBCs WBC casts
Renal tubular epithelial (RTE) cells RTE casts Pigmented casts
Granular casts
Eosinophiluria
Crystalluria
Prerenal
Postrenal
Arterial thrombosis or embolism
Preglomerular vasculitis
HUS or TTP
Scleroderma crisis
GN
Vasculitis
Malignant hypertension
Thrombotic microangiopathy
Interstitial nephritis
GN
Pyelonephritis
Allograft rejection
Malignant infiltration of the kidney
ATN
Tubulointerstitial nephritis
Acute cellular allograft rejection
Myoglobinuria
Hemoglobinuria
ATN
GN
Vasculitis
Tubulo-interstitial nephritis
Allergic interstitial nephritis
Atheroembolic disease
Pyelonephritis
Cystitis
Glomerulo-nephritis
Acute uric acid nephropathy
Calcium oxalate (ethylene glycol intoxication)
Drugs or toxins (acyclovir, indinavir, sulfadiazine, amoxicillin)

Figure; Interpretation of urinary sediment findings in acute kidney injury (AKI).

ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBCs, white blood cells.

- Serum electrolytes
- Abdominal ultrasound: to exclude urinary tract obstruction and assess kidney size
- Other investigation should be done based on the suspected specific cause
- Renal biopsy:

Treatment of AKI

Objectives of treatment

- Correct reversible causes of AKI
- Avoid worsening of kidney injury
- Maintain normal volume and electrolyte status
- Avoid overdoses of medications with renal clearance

- The management of individuals with and at risk for AKI varies according to the underlying cause
- Common to all are several principles

Non pharmacologic treatment

- **Maintain Fluid & electrolyte balance**
  - Strict fluid input and output chart or daily weighing
  - Decrease salt intake in fluid overloaded patients
  - Free water restriction in hyponatremia
  - Decrease foods rich in potassium

2. **Surgical intervention:** For obstructive uropathy
3. **Prevent further kidney injury**
   - Avoid nephrotoxic medications and radiocontrast agents
   - Adjust doses of medicines with renal clearance
   - Treat Heart Failure
4. **Dialysis**: if the patients live far from a hospital with dialysis service, referral should be made before the indications for dialysis develop.
   - **Indications for dialysis**
     - When medical management fails to control
       - volume overload (Pulmonary edema and anuria)
       - Severe hyperkalemia (> 6.5 mmol/l) or
       - Intractable metabolic acidosis
     - In some toxic ingestion
     - When there are severe complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding)

Pharmacologic treatment

- There is no specific pharmacologic treatment for AKI caused by ischemic or nephrotoxic acute tubular necrosis.
- The specific treatment depends on the cause of the AKI.
- **Intravenous fluids**
  - ✓ Indicated only in patients who are hypotensive or dehydrated on clinical evaluation.
  - ✓ In patients with hypovolemia or clinical hydration, fluids should be given to keep the fluid balance in the positive side.
  - ✓ Do not give (“challenge’) fluid for all patients unless there is evidence of volume depletion)
  - ✓ Urine output and fluid balance should closely followed as oliguric patients can easily develop pulmonary edema.
- **Furosemide**:
  - ✓ Indicated in patients with signs of fluid overload (edema, evidence of pulmonary congestion or high BP)
  - ✓ Starting dose 40mg, intravenously. If no response increase the dose every 1-2 hour till adequate response.
  - ✓ Do not go beyond 200mg/dose.
  - ✓ Doses above 100mg should be given diluted (1-2mg/ml of fluid) and given slowly (4mg/min).
    - ☛ E.g. 200mg in 100ml NS/01 hr, 160mg in 100mL NS/ 40min
  - ✓ Response can be considered adequate, if the urine output is 50-100ml in 01 hour, or 100-200ml in 02 hours.
- **Treatment of hyperkalemia** → Click and see section on Hyperkalemia
- **Treatment of hypertensive emergency** → see section on hypertension from chapter one (click here → Hypertension (የደም ግፊት) and HHD)
- **Treatment of specific cause**:

- The following patients with AKI need to be managed in a hospital with a nephrology and dialysis services.
  - ○ Worsening AKI despite efforts to manage the possible causes
  - ○ Glomerulonephritis considered to be the cause of AKI
  - ○ AKI of unknown etiology
  - ○ Any indications for dialysis

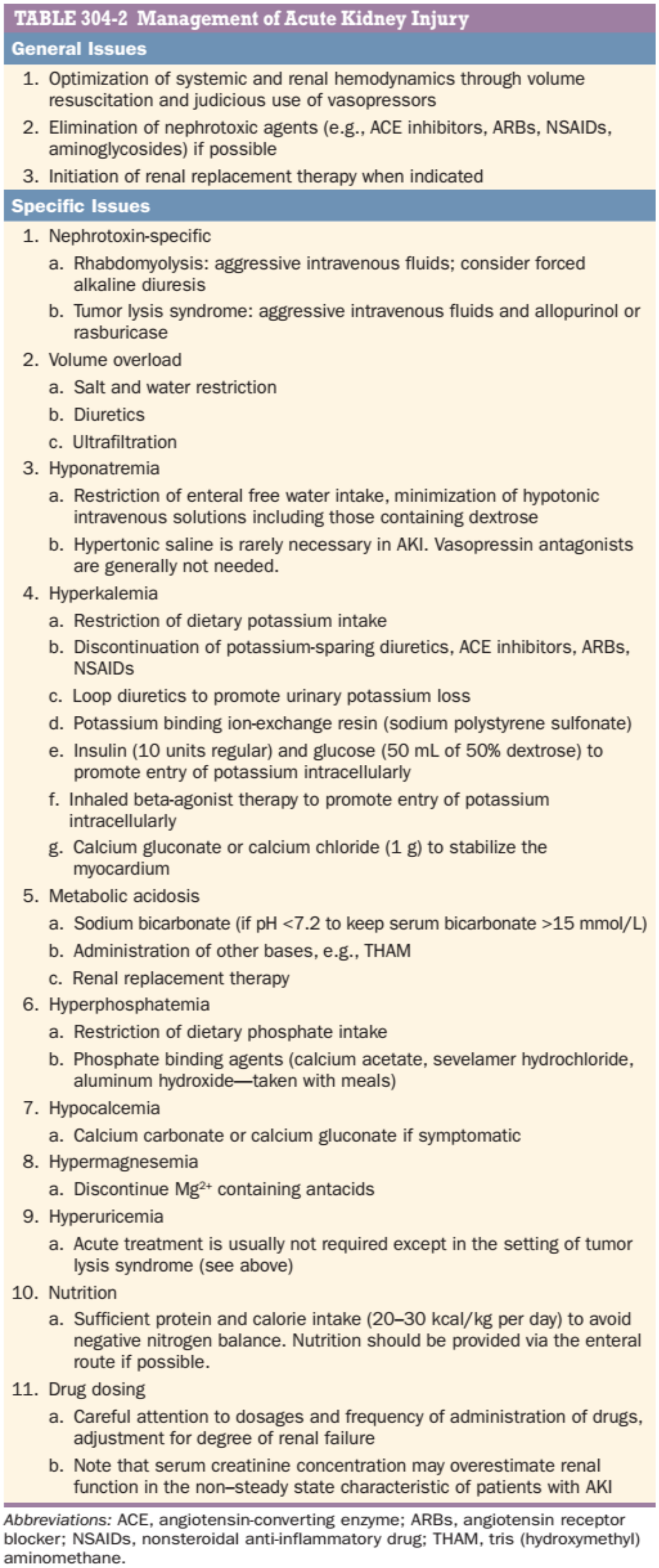


TABLE 304-2 Management of Acute Kidney Injury

General Issues

1. Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
2. Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides) if possible
3. Initiation of renal replacement therapy when indicated

Specific Issues

1. Nephrotoxin-specific
    - a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis
    - b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase
2. Volume overload
    - a. Salt and water restriction
    - b. Diuretics
    - c. Ultrafiltration
3. Hyponatremia
    - a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose
    - b. Hypertonic saline is rarely necessary in AKI. Vasopressin antagonists are generally not needed.
4. Hyperkalemia
    - a. Restriction of dietary potassium intake
    - b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs
    - c. Loop diuretics to promote urinary potassium loss
    - d. Potassium binding ion-exchange resin (sodium polystyrene sulfonate)
    - e. Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly
    - f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly
    - g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium
5. Metabolic acidosis
    - a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L)
    - b. Administration of other bases, e.g., THAM
    - c. Renal replacement therapy
6. Hyperphosphatemia
    - a. Restriction of dietary phosphate intake
    - b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
7. Hypocalcemia
    - a. Calcium carbonate or calcium gluconate if symptomatic
8. Hypermagnesemia
    - a. Discontinue Mg^{2+} containing antacids
9. Hyperuricemia
    - a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see above)
10. Nutrition
    - a. Sufficient protein and calorie intake (20–30 kcal/kg per day) to avoid negative nitrogen balance. Nutrition should be provided via the enteral route if possible.
11. Drug dosing
    - a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure
    - b. Note that serum creatinine concentration may overestimate renal function in the non–steady state characteristic of patients with AKI

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drug; THAM, tris (hydroxymethyl) aminomethane.

Prevention

- A significant proportion of AKI is preventable.

- Rapid and adequate fluid replacement in volume depleted patients
- Early detection and management of sepsis, malaria, pre-eclampsia
- Avoiding nephrotoxic medications in high risk patients, whenever possible e.g. NSAIDS, aminoglycosides, iodinated intravenous contrast agents.
- Close monitoring of renal function and urine output in hospitalized patients
- Dose adjustment of drugs with renal clearance.

Outcome and Prognosis

- **Prerenal azotemia carries a better prognosis than most cases of intrinsic AKI.**
    - Exception of the cardiorenal and hepatorenal syndromes, and postrenal azotemia
- The kidneys may recover even after severe, dialysis-requiring AKI.
- **Survivors of an episode of AKI requiring temporary dialysis, however, are at extremely high risk for progressive CKD**, and **up to 10% may develop ESRD** (end-stage renal disease).
- Post discharge care under the supervision of a nephrologist for aggressive secondary prevention of kidney disease is prudent.
- **Patients with AKI are more likely to die prematurely** after they leave the hospital even if their kidney function has recovered.

11.2 Chronic Kidney Disease (CKD)

- CKD is defined as the presence of kidney damage for more than 3 months as evidenced decreased GFR of < 60m/min or the presence of other markers of kidney damage with or without decreased GFR
- Other makers of kidney damage
    - Abnormalities on urinalysis: Persistent proteinuria is the most important one.
    - Abnormalities on imaging: shrunken kidneys, polycystic kidneys, hydronephrosis.
    - Histologic abnormalities findings on renal biopsy specimens
- CKD encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in GFR.
- The risk of CKD progression is closely linked to both the GFR and the amount of albuminuria.
- **For determination of estimated GFR** in adult patients with stable serum creatinine, use the MDRD (Modification of Diet in Renal Disease Study) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, which are freely accessible on line.

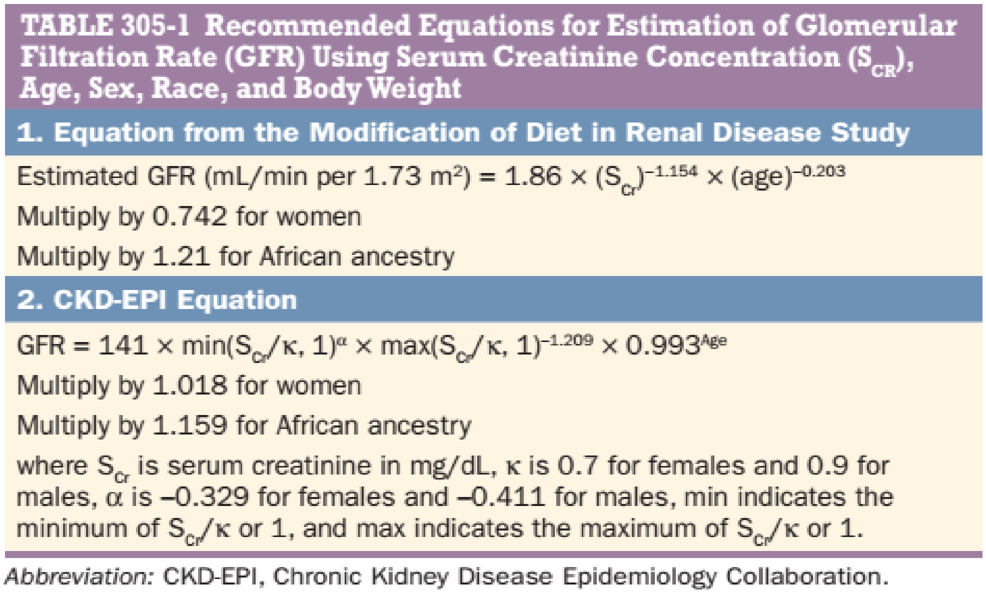


TABLE 305-1 Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (S_{CR}), Age, Sex, Race, and Body Weight

1. Equation from the Modification of Diet in Renal Disease Study

Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (\text{age})^{-0.203}$

Multiply by 0.742 for women

Multiply by 1.21 for African ancestry

2. CKD-EPI Equation

$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry

where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

- In our setup, during our internship, we were using **Cockcroft-Gault equation for GFR estimation, since it was easy for calculation (we used it from UpToDate 2018, we are not sure for the approval by KIDGO)**
  - Creatinine clearance (GFR) estimate by Cockcroft-Gault equation in adults and older adolescents (age ≥18 years).

$$GFR = \frac{(140 - age)\ x\ \ weight(in\ kg)}{72\ x\ serum\ creatinine\ level(in\ mg/dl)}$$

$$(multiply\ the\ result\ with\ 0.85\ for\ females)$$

- **The five most frequent causes of CKD**, cumulatively accounting for >90% of the CKD disease burden worldwide (Relative contribution of each category varies with geographic region and race)
  - Diabetic nephropathy
  - Glomerulonephritis
  - Hypertension-associated CKD
  - PCKD (polycystic kidney disease) / Autosomal dominant form/
  - Other cystic and tubulointerstitial nephropathy
- End stage renal disease (ESRD) → refers to a state of advanced CKD with estimated GFR being < 15ml/min where lifelong renal replacement therapy (dialysis or kidney transplantation) is necessary to sustain a reasonable quality of life and survival.

KDIGO (Kidney Disease Improving Global Outcome) classification of CKD

Table. KIDGO Classification of CKD based on CAG (cause, albuminuria and GFR)

GFR categories (ml/min/1.73 m^2) description and range

Categories (G)		**Description**	**GFR (ml/min/1.73m^2)**
G1		Normal or high	≥ 90
G2		Mildly decreased	60-89
G3	G3a	Mildly to moderately decreased	45-59
	G3b	Moderately to severely decreased	30-44
G4		Severely decreased	15-29
G5		Kidney failure	<15

Persistent albuminuria or proteinuria categories description and range

Category (A)	**Description**	**24hr urine albumin (mg)**	**24hr urine protein (mg)**
A1	Normal to mildly increased	< 30	<150
A2	Moderately increased	30-300	150-500
A3	Severely increased	>300	>500

CAUSE (C):

Determine possible cause by taking history, physical examination and doing relevant investigations.

- Diabetic Nephropathy
- Primary glomerular disease (Glomerulonephritis)
- Hypertension associated CKD
- PCKD
- Obstructive uropathy
- Autoimmune diseases

Clinical features

Symptoms

- Generally asymptomatic in the early stages (Stages 1 and 2 /i.e G1 and G2/CKD are usually asymptomatic)
- As CKD advances some non-specific symptoms might develop
- Common but nonspecific symptoms:
  - Nocturia
  - Fatigue
  - Loss of appetite, nausea, vomiting, hiccup
  - Weight loss
  - Muscle cramps, paresthesia
  - Pruritus
  - Body swelling, shortness of breath

  - Sleep disturbance, depression, anxiety, sexual dysfunction

Signs

- There are specific signs for CKD.
- Early stages of CKD might not have any signs apart from signs of the underlying disease
- Advanced stages
  - Edema, pleural effusion or crackles on lower lung field
  - Dry skin, excoriation marks, papular eruptions, uremic frost
  - Pericardial friction rub or distant heart sounds
  - Uremic fetor, decrement in cognition, flapping tremor, lethargy

Investigations and diagnosis

Diagnosis

- The diagnosis is of CKD is made based on the KDIGO criteria mentioned above.
- Once the diagnosis of CKD is established cause identification and staging should be made based on the CAG system (C-cause A-albuminuria level and G-GFR level).
- Example if a patient with CKD presumed to be due to diabetic kidney disease has eGFR of 40m/min and 24hr protein is 1200mg.

C= Diabetes G=G3b A= A3 (Stage: G3b A3 CKD due to diabetic kidney disease)

Investigations

- Serum creatinine and urea: Estimated GFR
- Urinalysis
- Quantification of proteinuria or albuminuria: 24urine protein/albumin, spot urine albumin to creatinine ratio (ACR)
- Abdominal ultrasound
- Calcium, Phosphate, PTH levels (preferably intact PTH level than total PTH)
- Alkaline phosphatase
- Serum electrolytes
- Abdominal ultrasound
- CBC

Estimated GFR (eGFR) should be used for follow up of patients with CKD than serum creatinine alone

Treatment of CKD

Objectives of treatment

- Slow the progression of decline in GFR
- Prevent, detect and manage complications
- Improve quality of life and survival

Principles of CKD management:

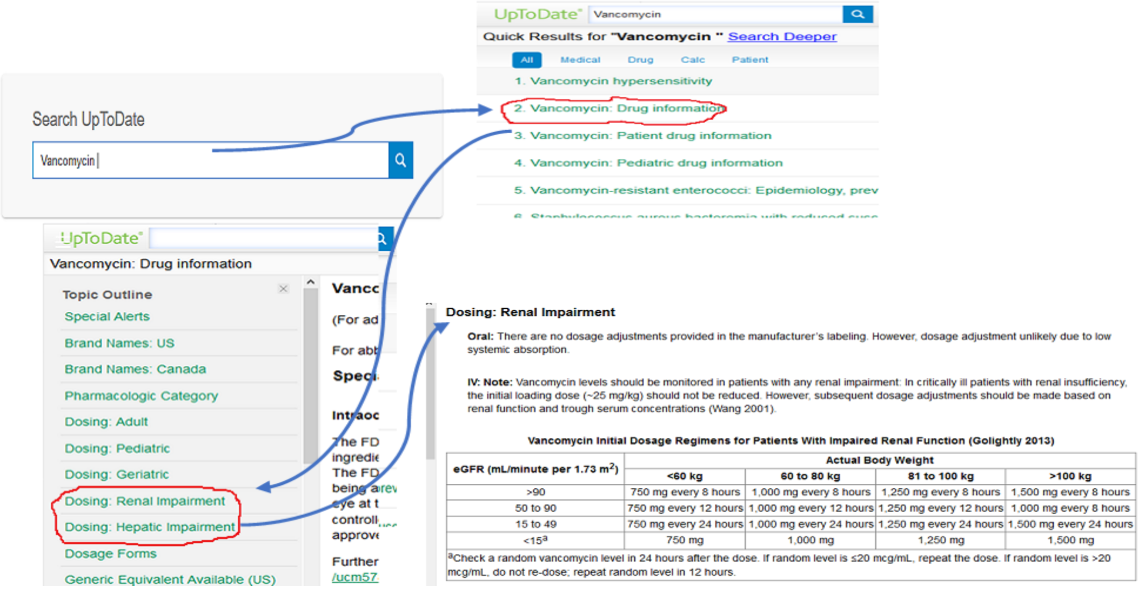
- Establish the cause of CKD and treat (if possible)
- Identify and manage unexpected (acute) deterioration in kidney function
- Preventing or slowing disease progression
- Treatment of the complications
- Identification and adequate preparation for RRT

1. Treatment of reversible causes

- Surgical management of Urinary tract obstruction
- Management of Fluid loss, sepsis etc.

2. Slowing the rate of progression

- General health advice e.g. smoking cessation, weight reduction for obese individuals
- Restrict salt intake
- Dietary protein reduction
    - Physicians should not overemphasize on protein restriction as the benefits are modest.
    - In malnourished individuals, which many advanced CKD patients are, protein restriction should not be advised.
- Medication Dose Adjustment
    - Some drugs that should be avoided include
        - Metformin and other oral anti-hyperglycemics that are eliminated by the kidney.
        - NSAIDs
        - Meperidine
    - Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval.
    - Several online Web-based databases for dose adjustment of medications according to stage of CKD or estimated GFR are available (e.g. *http://www.globalrph.com/ index_renal.htm*).
    - Or **you can search a specific drug dose adjustment for renal impairment, from UpToDate as shown in the picture below**


UpToDate
Vancomycin
Quick Results for "Vancomycin " Search Deeper
All
Medical
Drug
Calc
Patient
1. Vancomycin hypersensitivity
2. Vancomycin: Drug information
3. Vancomycin: Patient drug information
4. Vancomycin: Pediatric drug information
5. Vancomycin-resistant enterococci: Epidemiology, prev
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Vancomycin
UpToDate
Vancomycin: Drug information
Topic Outline
Special Alerts
Brand Names: US
Brand Names: Canada
Pharmacologic Category
Dosing: Adult
Dosing: Pediatric
Dosing: Geriatric
Dosing: Renal Impairment
Dosing: Hepatic Impairment
Dosage Forms
Generic Equivalent Available (US)

Dosing: Renal Impairment

Oral: There are no dosage adjustments provided in the manufacturer's labeling. However, dosage adjustment unlikely due to low systemic absorption.

IV: Note: Vancomycin levels should be monitored in patients with any renal impairment: In critically ill patients with renal insufficiency, the initial loading dose (~25 mg/kg) should not be reduced. However, subsequent dosage adjustments should be made based on renal function and trough serum concentrations (Wang 2001).

Vancomycin Initial Dosage Regimens for Patients With Impaired Renal Function (Golightly 2013)

eGFR (mL/minute per 1.73 m^2)	Actual Body Weight			
	<60 kg	60 to 80 kg	81 to 100 kg	>100 kg
>90	750 mg every 8 hours	1,000 mg every 8 hours	1,250 mg every 8 hours	1,500 mg every 8 hours
50 to 90	750 mg every 12 hours	1,000 mg every 12 hours	1,250 mg every 12 hours	1,000 mg every 8 hours
15 to 49	750 mg every 24 hours	1,000 mg every 24 hours	1,250 mg every 24 hours	1,500 mg every 24 hours
<15[a]	750 mg	1,000 mg	1,250 mg	1,500 mg

[a]Check a random vancomycin level in 24 hours after the dose. If random level is ≤20 mcg/mL, repeat the dose. If random level is >20 mcg/mL, do not re-dose; repeat random level in 12 hours.

Picture; diagrammatic example on, how to search, **a specific drug dose adjustment for renal impairment, from UpToDate**

- Nephrotoxic radiocontrast agents and gadolinium should be avoided or used according to strict guidelines when medically necessary

Treatment and control of hypertension

- **Target blood pressure < 130/80 mmHg**
- **First line: ACE inhibitors or angiotensin receptor blockers (ARBs)**…see section on hypertension from chapter one for the options (click here → Hypertension (የደም ግፊት) and HHD).
  - Avoid ACE inhibitors/ARBs if patient has hyperkalemia.
  - Serum creatinine and potassium should be followed one to two weeks following initiation or dose increment.
  - If serum potassium or creatinine can't be followed, don't start ACE inhibitors/ARBs in patients with CKD.
  - Up to 20-30% increment in creatinine is expected; hence, if the rise in creatinine is less than 30%, the ACEi/ARB needs to be continued with close monitoring. If the increase is above 30% or <30% but progressively increasing, the drug should be discontinued.
- **Add-on and Alternatives**
  - If BP is not controlled to the target with ACE inhibitors/ARBs or ACE inhibitors are contraindicated, add or replace by other antihypertensive.
  - Long acting **calcium channel blocker (CCB)**: Amlodpine or sustained/extended release Nifedipine OR
  - **Loop diuretics** (if eGFR is ≤30m/min) or **thiazide diuretics (if GFR>30ml/min)** OR
  - A combination of long acting CCB and diuretics (loop or thiazide, based on the eGFR)
  - If the above three (ACEi/ARB + CCB + diuretic) or two (CCB + Diuretic) fail achieve target BP add a **beta-blocker.**

- **Treatment and control of proteinuria**
    - **First line**
        - ACE inhibitors or ARBs.
            - **ACE inhibitors** (particularly Enalapril) are preferred over ARBs due to their low cost and wide availability

First line

- **Enalapril:** starting dose 5mg BID, Maximum dose 20mg BID…

Alternatives

- **Lisinopril:** starting dose 5mg/day, Maximum dose 40mg/day
- **Perindopril:** starting dose 5mg/day. Maximum dose 15mg/day

ARB's

- **Telmisartan:** Starting dose: 40mg/day maximum dose 80mg/day
- **Irbesartan**: Starting dose: 75-150mg/day, maximum dose 300mg/day
- **Losartan:** Starting dose 50mg/day maximum dose 100mg/day
- **Valsartan:** Starting dose 80 -160mg/day, maximum dose 320mg/day
- **Candesartan:** Starting dose 8-16mg/day maximum dose 32mg/day

- **Control of hyperglycemia in Diabetes**
    - In early CKD good blood sugar control is essential and helps to decrease progression of CKD.
    - In advanced CKD (Stage G4 and above or in patients on dialysis) the risk of hypoglycemia is very high and tight glycemic control should be avoided.
    - Although individualization based on age, expected survival, rates of hypoglycemia, additional comorbidities is need, in patients with eGFR<30ml/min a HbA1C target of about 7.5% is acceptable (if achieved without significant hypoglycemia)
    - In patients with advanced CKD eGFR <30ml/min
        - Metformin should be discontinued.
        - Long acting sulfonylureas (particularly the commonly used Glibenclamide) should be avoided.
        - nsulin based therapy is preferred.

3. Treatment of the complications

- **Treatment of anemia of CKD**

- Indications to start treatment: Hemoglobin < 10g/dl or symptomatic.
- **Iron**
    - Serum iron studies: Ferritin and transferrin saturation (TSAT) helps to guide iron therapy

      $$\mathrm{TSAT} = \frac{\text{Serum iron}}{\text{TIBC}}\ X\ 100\%,$$ TIBC = Total Iron binding capacity
    - TSAT < 20% should be treated with iron.
    - If iron studies cannot be done, most patients with CKD are iron deficient and should be started on therapeutic iron.
    - Ferritin can be high even in iron deficient CKD patients; hence high ferritin should not be a reason to differ iron.
    - Preferred: Intravenous iron
- **Iron sucrose**
    - **For patients not on hemodialysis:**
        - **Iron sucrose** 200mg, IV, administer over 5 minutes, every 3 days for a total of 5 doses (a total of 1000mg). This dose is usually sufficient but if hemoglobin is not corrected, additional doses can be given. OR
        - **Iron sucrose** 200mg diluted in 100ml NS; administer over 30 minutes.
    - **For patients on hemodialysis**
        - **Iron sucrose** 100mg, IV, over 2-5 minutes, given early during dialysis sessions (within the first hour) until iron deficiency is corrected. It needs to be given again, if iron deficiency persists or recurs.
    - Alternative: Options
        - **Ferrous sulfate,** 325mg (65mg elemental iron) before meal OR
        - **Ferrous gluconate**, 325mg P.O. (39mg elemental iron), 1-2tabs, TID OR
        - **Ferrous fumarate**, 325mg P.O., (107 elemental iron), one tab, daily to twice per day.
    - For patients who do not tolerate ferrous sulfate tablets, they may be advised to take it with meals, or to take a smaller dose, or elixir (solution) forms.
        - **Iron hydroxide polymaltose syrup** (Each 5ml contains 50mg elemental iron), 10ml PO, BID to TID. OR
        - **Ferrous gluconate syrup** (Each 5ml contains 24mg elemental iron), 15ml, PO TID.OR
        - **Ferric ammonium citrate syrup** (Each 15ml contains 32.8mg elemental iron), give 30ml, TID.

Erythropoiesis stimulation agents (ESA):

- **Epoetin (alpha/beta)**
  - **Initiate if Hemoglobin is < 10g/dl after iron therapy.**
  - CKD patients **on hemodialysis**
    - Initial dose: 4000IU, IV, 3 times a week
  - CKD patients **not on dialysis**
    - Initial dose: 4000IU, SC, 3 times a week
  - Dosage adjustments for CKD patients (either on dialysis or not on dialysis):
  - Do not increase dose more frequently than every 4 weeks (dose decreases may occur more frequently).
    - If hemoglobin does not increase by >1 g/dl after 4 weeks: Increase dose by 25%
    - If hemoglobin increases >1 g/dl in any 2-week period: Reduce dose by 25-50%

- **Treatment of hyperphosphatemia:**
  - Phosphate binders are indicated if serum phosphorus is > 5.5mg/dl

First line

- Sevelamer (as hydrochloride or carbonate)
  - Initial dose 800mg, PO, TID with meal. If serum phosphorus >9mg/dl, 1600mg, PO TID can be started.
  - Adjust the dose to target to a target serum phosphorus near normal (< 5.5mg/dl)

Alternative:

- Calcium carbonate: starting dose 500 - 1000mg, PO, TID, chew, with meal
- Calcium acetate: starting dose 1334mg, PO, TID with meal
- If total serum calcium increase >10mg/dl: hold calcium
- If there is hypocalcemia, calcium-based phosphate binders are preferred over sevelamer.

- **Treatment of secondary hyperparathyroidism**
  - The main stay of treatment is correcting phosphorus and serum calcium
  - Serum PTH (preferably intact PTH) should not be overcorrected: 2-9 times the upper limit of normal is acceptable.
  - If PTH level is above nine times the upper limit after correction of phosphorus and calcium use either of the following: Calcitriol or synthetic vitamin D analog (alfacalcidol or paricalcitol).
    - Alfacalcidol: starting dose 2.5 to 5 µg/day. OR
    - Paricalcitol: starting dose 1 µg/day or 2 µg 3x/week. OR
    - Calcitriol: 0.25 - 0.5 µg /day

- **Treatment of fluid overload (edematous state)**
  - Furosemide, 40-120mg, PO/IV, BID or TID.

  - Higher dose and more frequent dosing intervals are required in advanced CKD.

- **Treatment of hyperkalemia** → click and see section on Electrolyte disturbance, sub-section Hyperkalemia from short case of Nitsbin

4. Identification and adequate preparation for RRT

- Renal replacement therapy (RRT) for ESRD: Dialysis and kidney transplantations are the options
  - Renal transplantation is the preferred modality of RRT
  - Preemptive kidney transplantation is preferable (Before initiating dialysis)
- Indications for RRT
  - For preemptive kidney transplant: patients with GFR <20ml/min are candidates
  - For dialysis
    - Patients with GFR<15ml/min and symptomatic
    - Starting dialysis based on low GFR alone without symptoms is not beneficial.

N.B. All AKI/CKD Patients need nephrologist evaluation. But, in the following conditions, Nephrologist intervention in referral setup is mandatory.

- Patients with known causes of CKD (e.g. diabetic kidney disease, obstructive uropathy) when the GFR is less than 30ml/min.
- If the cause of CKD is not known or suspected to be glomerular disease

Chapter 12; Glomerular disease (Nephrotic syndrome and Nephritic syndrome)

Dr. Mulualem. G

12.1 Nephrotic syndrome (NS)

- **Nephrotic syndrome (NS)** is a clinical sate which results from heavy (massive) proteinuria.
- The presence of nephrotic syndrome (NS) is a definitive indicator of glomerular pathology.
- Nephrotic syndrome is defined if all the following 1st three clinical and laboratory findings are fulfilled
  1) **Heavy proteinuria**: defined as urine protein >3000mg (3gm) in a 24hr urine protein
  2) **Hypoalbuminemia:** Defined as serum albumin <3g/dl
  3) **Edema/anasarca**
  4) Hyperlipidemia (hypercholesterolemia) → usually severe, is a common finding. Some experts include it as requirement for the diagnosis of NS..
  5) Hypertension
  6) Minimal microscopic hematuria;
- **Notice**
  - **Proteinuria (nephrotic range) and edema are marked in nephrotic syndrome than nephritic syndrome**
  - **Hypertension and Hematuria are marked in nephritic syndrome than nephrotic syndrome**
- Some patients might have heavy proteinuria (>3000mg in 24-hour urine) but do not have the other features of the NS. They are said to have **nephrotic range proteinuria**, but not the nephrotic syndrome.
- If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure
- The GFR in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years.
- Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome) associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine.
- Increased susceptibility to infection, venous thrombosis, and acute kidney injury are the major complications of the NS.

- Nephrotic syndrome is not a single disease. It is a manifestation of several diseases. Hence, once the presence of NS is confirmed, the etiology should be identified.
- Nephrotic syndrome in adults is different from pediatric NS in etiology, the needed investigation, treatment, and outcome. Hence, **adult NS should never be treated like pediatric NS.**
- The causes of nephrotic syndrome are classified in to two major groups: **Primary** (diseases limited to the glomeruli) and **secondary** (systemic diseases with glomerular manifestations or complications)
- Diabetes (diabetic kidney disease) is the leading cause of nephrotic range proteinuria worldwide.

Table. Major causes of nephrotic syndrome in adults

Major cause of primary nephrotic syndrome	Major causes of secondary nephrotic syndrome
➢ Primary Focal segmental glomerulosclerosis (FSGS) ➢ Minimal change disease (MCD) ➢ Primary membranous nephropathy (MN) ➢ Primary membranoproliferative glomerulonephritis (MPGN)	➢ Diabetic Nephropathy ➢ Autoimmune disease: SLE ➢ Infectious: HBV, HCV, HIV, Syphilis, Schistosomiasis ➢ Amyloidosis: primary or secondary amyloidosis ➢ Drugs: NSAIDS ➢ Preeclampsia ➢ Malignancy: Multiple myeloma, lymphoma, carcinomas

Clinical features

Symptoms and signs

- **Symptoms and signs related to the nephrotic state**
    - **Body swelling:** Periorbital edema, peripheral edema, scrotal or labial edema
    - **Third space fluid collection:** ascites, pleural effusion
    - **Fatigue and shortness of breath**
    - **Urine:** excessive foaming
    - **Nail:** white horizontal bands on the nail
- **Clinical features suggestive of specific secondary causes**
    - **Diabetes:** Known history of diabetes, presence of diabetic retinopathy
    - **SLE:** diffuse non-scarring hair loss, malar rash, photosensitivity, polyarthritis
    - **Preeclampsia:** third trimester pregnancy or peripartal state with high BP
    - **Multiple myeloma:** bone pain, pathological fracture, anemia
    - **Lymphoma:** Lymphadenopathy, splenomegaly
    - **Carcinomas:** Local symptoms (breast lump, abdominal mass, cough/hemoptysis, lymphadenopathy)

Diagnosis and investigation

Diagnosis

The following steps are helpful in guiding the diagnosis of nephrotic syndrome in adults

Step 1: Confirming the presence of nephrotic syndrome:

- 24-hour urine protein
- Serum albumin
- Lipid profile

Step 2: Investigation for common causes of nephrotic syndrome

- **Retinal screening** for diabetic retinopathy: any time for type 2 diabetics and after a minimum of five year of type 1 diabetes
- **HBSAg, HCV antibody, HIV screening, VDRL(RPR), ANA**
- **AntiPLA2R antibody**: For screening primary membranous nephropathy
- **Work up for multiple myeloma:** If suspected, serum free light chains and serum electrophoresis.
- **Work up for other malignancies**: only if there are clinical clues.

Step 3: Renal biopsy

- Unlike pediatric patients almost all non-diabetic adult patients with nephrotic syndrome need renal biopsy to confirm the etiology. Hence, they need to be referred to a hospital with nephrology service.

Investigations: **Additional helpful investigations**

- **Urinalysis**: hematuria and proteinuria
  - Hematuria can be gross or microscopic hematuria. More common in nephritic syndrome than nephrotic syndrome
  - In early nephropathy, such as in diabetic nephropathy, proteinuria increases to 30 - 300 mg/24 h and is called microalbuminuria and represents the presence of renal disease.
  - Greater than 300 mg/24 h of albuminuria represents frank proteinuria and more advanced renal disease

Table; Urine Assays for Albuminuria/Proteinuria

	24h Albumin (mg/24hr)	24h Albumin (mg/24hr)	Albumin to creatinine ratio (mg)	Dipstick proteinuria
Normal	8 - 10	<150	<30	—
Microalbuminuria	30 - 300	—	30 - 300	-/Trace/1+
Proteinuria	>300	>150	>300	Trace - 3+

- **Renal function tests (serum creatinine):** AKI can occur as a complication of the NS or over-diuresis or could be part the glomerular disease (nephrotic-nephritic presentation)
- **Serum electrolytes:** As baseline for diuretic therapy
- **Abdominal ultrasound**: to see kidney sizes
- **Investigations when complications are suspected**: e.g. if deep vein thrombosis (a common complication is suspected), do doppler ultrasound of suspected limb veins.

Treatment

Non-pharmacologic treatment

- Salt restriction
- Fluid restriction (less than 1 - 1.5 liter/day)
- Encourage ambulation
- Protein should not be restricted rather encourage patients to take adequate protein and high calorie diet

Pharmacologic treatment

1. **Treatment of the edematous state**
   - **Loop diuretics:** nephrotic syndrome is associated with relative diuretic resistance
     - **Oral Furosemide:**
       - Starting dose 40mg, PO, BID -TID.
       - Increase the dose to 80 mg PO BID-TID, then 120mg. PO, BID-TID.
     - **Aim**: decrease weight by 0.5 to 1kg/day.
     - **IV Furosemide:** If no adequate weight loss with increasing dose, admit for IV Furosemide
       - Start with 40mg, IV, TID.
       - Increase the dose to 80 mg IV TID, then 120mg. PO, TID
       - If no adequate response with IV Furosemide, add **hydrochlorothiazide 12.5 to 25mg BID** (to be given 30 minutes before the IV Furosemide)
     - Add prophylactic **KCl tablets (600mg BID-TID) or Spironolactone 25-50mg** PO/daily and monitor serum electrolytes every 2-3days.
2. **Anti-proteinuric treatment**
   - **ACE inhibitors or Angiotensin receptor blockers (ARBS)**
     - Start after adequate diuresis.
     - The kidney function must be stable before starting.
     - The dose should be escalated gradually with monitoring of serum creatinine and potassium. Monitoring should be done within 2 weeks of initiation and dose escalation.
     - ACE inhibitors (particularly Enalapril) are preferred over ARBs due to their low cost and wide availability.

Preferred

- **Enalapril:** starting dose 5mg BID, Maximum dose 20mg BID

Alternatives

- **Lisinopril**: starting dose 5mg/day, Maximum dose 40mg/day
- **Perindopril**: starting dose 5mg/day. Maximum dose 15mg/day

ARB

- **Telmisartan**: Starting dose: 40mg/day maximum dose 80mg/day
- **Irbesartan**: Starting dose: 75-150mg/day, maximum dose 300mg/day
- **Losartan**: Starting dose 50mg/day maximum dose 100mg/day
- **Valsartan**: Starting dose 80 -160mg/day, maximum dose 320mg/day
- **Candesartan**: Starting dose 8-16mg/day maximum dose 32mg/day

3. **Pharmacologic treatment for complications of the nephrotic syndrome**

- **Treatment of hyperlipidemia**: as per dyslipidemia treatment guideline (see section on dyslipidemia). Many patients require statins due to sever hyperlipidemia.
- **Prophylactic anticoagulation**: Indicated if serum albumin is <2g/dl and patient is hospitalized
    - **UFH, 5,000IU, BID** until discharge Or
    - **Enoxaparin 40mg, SC, daily** until discharge
- **Therapeutic (Full dose) anticoagulation: Indications**
    - If there is active venous thromboembolic disease (e.g. DVT/PE, renal vein thrombosis)
    - If albumin is low and the following risk factors are found: Pregnancy, active malignancy, recent major surgery, NYHA class III or IV heart failure or morbid obesity
        - **UFH, 17,500 SC, BID or Enoxaparin 1mg/kg/dose BID + Warfarin,** 2 to 5 mg PO daily (dose to be adjusted according to INR, usual maintenance dose ranges from 2 to 10 mg daily)
        - **Overlap heparin with warfarin** until two therapeutic INRs (2-3) achieved, and then followed by Warfarin alone.
        - **Duration of anticoagulation**: Until the nephrotic syndrome resolves or 6-12 months (if it does not resolve).

4. **Treatment of the specific cause of the nephrotic syndrome**

- **Empiric steroid or any immunosuppressive should not be started** for adults with nephrotic syndrome without doing renal biopsy; hence, all adult patients with non-diabetic nephrotic should be referred to a hospital with nephrology service.

12.2 Nephritic syndrome

- **Acute nephritic syndromes** classically present with
    - **Hypertension**
    - **hematuria with red blood cell casts**
    - **pyuria, and**
    - **mild to moderate proteinuria** (1 - 2 g/24 h**).**
- Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension
- If glomerular inflammation develops slowly, the serum creatinine will rise gradually over many weeks, but if the serum creatinine rises quickly, particularly over a few days, acute nephritis is sometimes called *rapidly progressive glomerulonephritis* (RPGN)
    - The histopathologic term *crescentic glomerulonephritis* is the pathologic equivalent of the clinical presentation of RPGN.

Table; Causes of Nephritic syndrome

- **PSGN (Poststreptococcal glomerulonephritis)** [a]
    - The most common forms of glomerulonephritis in our setup especially in children. In adults, post infectious Glomerulonephritis (PIGN) is common cause
- **IgA nephropathy** [a]
    - The most common forms of glomerulonephritis worldwide
    - Previously termed as Berger disease (from the scientist who first described the glomerulonephritis)
- Systemic causes
    - **Subacute bacterial endocarditis** [a]
    - **Lupus nephritis** [a]
- **Antiglomerular basement membrane disease** [a]
- **Membranoproliferative glomerulonephritis** [a]
- **Mesangioproliferative glomerulonephritis**
- **Henoch-Schönlein purpura** [a]
- Cryoglobulinemia [a]
- C_3 Glomerulopathies
- ANCA small-vessel vasculitisa
    - Granulomatosis with polyangiitis (Wegener's)
    - Microscopic polyangiitis
    - Churg-Strauss syndrome

[a] **Can present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis.**

Acute glomerulonephritis (AGN) and rapidly progressive glomerulonephritis (RPGN)

- **Acute glomerulonephritis (AGN) and rapidly progressive glomerulonephritis (RPGN)** are important causes of AKI. in that they have clearly identifiable clinical features and can rapidly progress to ESRD
- AGN and RPGN present more or less in a similar fashion. Their presentation is commonly described as the **nephritic syndrome**.
- The clinical difference between AGN and RPGN: It is not easy to clinically differentiate between the two.
    - In RPGN: The kidney function keeps of deteriorating over days to weeks, unless treated. It progresses to ESRD unless treated early.
    - In infection related AGN: The kidney function usually improves.
- **The most common causes of self-limiting AGN are bacterial infections (also called infection related glomerulonephritis).**

- As opposed to pediatric AGN, where the commonest cause is streptococcal infection of the skin or the throat, adult AGN can occur following any bacterial infection at any site.
- The most important causes of RPGN are **autoimmune diseases:** SLE (systemic lupus erythematosus), systemic small vessel vasculitis (ANCA-vasculitis), antibody direct to glomerular basement membrane (Anti-GBM disease).
- The histopathologic finding in both AGN and RPGN is described as diffuse proliferative glomerulonephritis (DPGN) and crescentic glomerulonephritis respectively.

Clinical features

- **Clinical features of the AGN/RPGN: the nephritic syndrome**
  - Acute onset body swelling (Edema) and shortness of breath
  - Decreased urine amount (oliguria)
  - Reddish urinary discoloration (typically tea or cola colored urine)
  - High blood pressure
- **Clinical features of suggesting the underlying causes (systemic diseases)**
  - Hair loss/diffuse non-scaring alopecia — SLE
  - Malar rash, photosensitive rash, non-pruritic rash over the body— SLE
  - Joint pain, evidence of arthritis (swelling and tenderness of joints) — SLE
  - Hemoptysis, cough and dyspnea — Vasculitis, Anti-GBM disease or pulmonary edema
  - Petechiae/purpura — Vasculitis or SLE
  - Pleural effusion — Part of the complication or SLE associated
  - Pericarditis (friction rub or distant heart sound) — SLE or uremic pericarditis
  - Cardiac murmurs — Infective endocarditis or SLE
  - Focal neurologic deficit — SLE (Lupus cerebritis) or vasculitis
- **Clinical features related to marked decrement in the kidney function**
  - Pulmonary crackles — pulmonary congestion
  - Nausea and vomiting — uremic gastropathy
  - Change in mental status — uremic or hypertensive encephalopathy
  - Mucocutaneous bleeding — uremic bleeding

Diagnosis and investigations

Diagnosis

- The diagnosis of AGN or RPGN should be made clinically in any patient presenting with the nephritic syndrome (acute onset body swelling, tea/cola colored urine, oliguria, and high BP)
- Further investigations are needed for three purposes: For confirming the nephritic syndrome, for identifying possible etiologies, and complications.

Investigations

i. Investigation for evidencing the presence of the nephritic syndrome (AGN/RPGN)

- **Urinalysis:**
  - Hematuria and proteinuria
  - The RBCs in the urinalysis: Significant proportion are dysmorphic
  - RBC casts: may or may not be present. Their presence is not mandatory for diagnosis)
- **24hour urine protein:** above 500mg (usually>1000mg), it can sometimes be nephrotic range(>3000mg)
- **Serum creatinine and ureaii**

ii. Investigations for assessing potential complications

- **Serum electrolytes:** particularly serum potassium (to look for hyperkalemia).
- **Chest X-ray:** for evidence of pulmonary edema or pleural effusion.

iii. Investigations for identifying possible etiology

- **Basic serologies: to be done at initial evaluation**
  - **Anti-streptolysin titer (ASO)**: For preceding streptococcal infection
    - It may be falsely low or negative in patients with skin infections.
    - It remains a useful test in those with pharyngitis but antibiotics may decrease the titer
  - **The streptozyme test**
    - It is a much better than ASO alone (has high sensitivity and specificity) for checking a preceding streptococcal infection.
  - Hepatitis B (HBV) and C (HCV) serology: HBSAg and HCV antibody.
  - HIV screening
  - ANA (anti-nuclear antibody)

- **Additional important diagnostic investigations**: to be ordered by specialist who would decide on definitive management
  - Anti-double strand DNA antibody(anti-dsDNA)
  - Anti-neutrophil cytoplasmic antibody test (ANCA)
  - Anti-glomerular basement antibody (Anti-GBM antibody)
  - Serum complement level (complement -3 and 4/C3 and C4 levels)
  - Renal biopsy

iv. Investigation for looking evidence of chronicity

- **Abdominal ultrasound:** bilateral small kidneys in adults (<9cm longitudinally) indicate chronic kidney disease. Normal or increased kidney size can be found in both acute and chronic glomerular diseases.

Treatment

Non-pharmacologic treatment

- Salt and fluid restrictions

- Dialysis: if there are indications (see the topic acute kidney injury for indications)

Pharmacologic treatment

1. Supportive (symptomatic) management

- **Loop diuretics**
  - **Oral Furosemide:**
    - For patients with mild peripheral edema.
    - Starting dose 40mg PO BID.
    - Follow every 2-3 days, increase the dose to higher dose (Maximum dose 600mg/day) or admit for IV diuresis, if response is suboptimal or there is worsening.
  - **IV Furosemide:**
    - For patients with pulmonary congestion or sever edematous state
    - Start with 40mg IV, stat. See response every 2 hours. If urine output of 150ml and above is achieved in 2 hours and give the 40mg IV BID or TID.
    - If urine output is <150ml in 2hours, increase the dose by 40mg and reassess the urine output in another 2 hours.
    - Give the dose which resulted in adequate once diuresis (>150ml/2hour) as standing e.g. 80mg or 120 IV BID or TID. Maximum bolus dose 200mg.
    - IV Furosemide above 100mg should be given slowly (over 15-20minutes)
  - **Avoid prophylactic potassium tablet or spironolactone:** due to the risk of hyperkalemia in patients with AGN/RPGN.

- **Antihypertensives**
  - **Loop diuretics** are the preferred Antihypertensives: see above on diuretic
  - **Additional Antihypertensive:** If BP is not well controlled with loop diuretics alone
    - **Add Calcium channel blocker on loopr diuretics:**
      - **Amlodpine** 5-10mg PO once daily OR
      - **Nifedipine** 20-40mg PO BID.
    - **If a third agent is needed** (on top of Furosemide and Calcium channel blocker combination) add a beta-blocker:
      - **Carvedilol** 6.25 to 25mg BID or
      - **Bisoprolol** 2.5 to10mg/day or
      - **Metoprolol** 25-100mg/day or
      - **Atenolol** 25-100mg/day
    - **Avoid ACE inhibitors, Angiotensin receptor blockers (ARBS):** due to the risk of hyperkalemia and potential for deterioration in kidney function.
    - **Avoid Spironolactone** in patients with AGN/RPGN: due to risk of hyperkalemia and worsening kidney function.

- **Management of hyperkalemia**
  - Start shifting treatment with regular insulin if serum potassium is >6.0mmol/l
    - **Regular Insulin:** 10IU regular insulin IV, immediately followed by 03vials (60ml) of 40% dextrose IV, to be given every 6 hour. Monitor blood sugar every 4-6 hourly.
    - If potassium is >7mmol/l or there are ECG changes hyperkalemia start IV calcium
      - **Calcium gluconate (10%) 10ml,** IV, to be given over 5 minutes followed by regular insulin (as above).

2. **Definitive management of the underlying cause**

- Definitive management of the underlying cause might require early initiation of intensive immunosuppressive therapy; hence, patients should be referred to nephrologist as soon as possible.

Poststreptococcal glomerulonephritis (PSGN)

- PSGN is prototypical for *acute endocapillary proliferative glomerulonephritis*.
- The incidence of PSGN has dramatically decreased in developed countries and in these locations is typically sporadic.
- **Acute PSGN in underdeveloped countries is epidemic and usually affects children between the ages of 2 and 14 years,** but in developed countries is more typical in the elderly, especially in association with debilitating conditions.
  - ✓ **It is also common in our setup especially in children**
- It is more common in males, and the familial or cohabitant incidence is as high as 40%.
- **Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease**
  - ✓ **PSGN due to impetigo develops 2 - 6 weeks after skin infection and 1 - 3 weeks after streptococcal pharyngitis.**
- PSGN is an immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury.

Clinical features

- **The classic presentation** is an acute nephritic picture with
  - Hematuria
  - Pyuria
  - Red blood cell casts

  - Edema
  - Hypertension, and
  - Oliguric renal failure
- Symptoms and signs may be severe enough to appear as RPGN.
- Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) in as many as 50% of cases.
- 5% of children and 20% of adults have proteinuria in the nephrotic range
- A subclinical disease is reported in some series to be 4 - 5 times as common as clinical nephritis, and these latter cases are characterized by asymptomatic microscopic hematuria with low serum C3 complement levels.

Investigations

- In the first week of symptoms, 90% of patients will have a depressed CH50 and decreased levels of C3 with normal levels of C4.
- Positive rheumatoid factor (30 - 40%)
- Positive cultures for streptococcal infection (10—70%)
- Increased titers of ASO (30%), anti-DNAse (70%), or antihyaluronidase antibodies (40%) can help confirm the diagnosis.

Treatment

- Treatment is **supportive**, with control of hypertension, edema, and dialysis as needed.
- **Antibiotic treatment** for streptococcal infection should be given to all patients and their cohabitants.
- There is no role for immunosuppressive therapy, even in the setting of crescents.

Prognosis and outcomes

- Recurrent PSGN is rare despite repeated streptococcal infections.
- Early death is rare in children but does occur in the elderly.
- Overall, the prognosis is good, with permanent renal failure being very uncommon in the past (<1%) but with recently, an increased risk of CKD in adulthood.
- Complete resolution of the hematuria and proteinuria in the majority of children occurs within 3-6 weeks of the onset of nephritis but 3-10% of children may have persistent microscopic hematuria, non-nephrotic proteinuria, or hypertension.
- The prognosis in elderly patients is worse with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and ESRD.

IgA nephropathy

- Berger first described the glomerulonephritis now termed *IgA nephropathy*.
- It is **classically characterized by episodic hematuria associated with the deposition of IgA in the mesangium.**
- **IgA nephropathy is one of the most common forms of glomerulonephritis worldwide.**
- There is a male preponderance, a peak incidence in the 2nd and 3rd decades of life, and rare familial clustering.
- IgA nephropathy is predominantly a sporadic disease but susceptibility to it has been shown uncommonly to have a genetic component depending on geography and the existence of "founder effects."
- Clinical and laboratory evidence suggests **close similarities between Henoch-Schönlein purpura and IgA nephropathy**.
- **Henoch-Schönlein purpura** is distinguished clinically from IgA nephropathy by
    - **prominent systemic symptoms**
    - **a younger age (<20 years old)**
    - **preceding infection, and**
    - **abdominal complaints.**
- Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including
    - CLD
    - Crohn's disease
    - GI adenocarcinoma
    - chronic bronchiectasis
    - idiopathic interstitial pneumonia
    - leprosy
    - ankylosing spondylitis
    - Sjögren's syndrome.
- IgA deposition in these entities is not usually associated with clinically significant
- glomerular inflammation or renal dysfunction and thus is not called IgA nephropathy.
- **IgA nephropathy is an immune complex—mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity.**
- A second hit, such as a viral or other antigen exposure, may be necessary for disease manifestation.
- Despite the presence of elevated serum IgA levels in 20 - 50% of patients, and IgA deposition in skin biopsies in 15 - 55% of patients, **a renal biopsy is necessary to confirm the diagnosis**.

Clinical features

- The two most common presentations of IgA nephropathy are
    - ✓ recurrent episodes of **macroscopic hematuria** during or immediately following an upper respiratory infection often accompanied by proteinuria or
    - ✓ persistent asymptomatic **microscopic hematuria.**
- Nephrotic syndrome is uncommon.
- Proteinuria can also first appear late in the course of the disease.
- Rarely patients present with acute renal failure and a rapidly progressive clinical picture.

- IgA nephropathy is a benign disease for the majority of patients, and 5 - 30% of patients may go into a complete remission, with others having hematuria but well-preserved renal function.
- In the minority of patients who have progressive disease, progression is slow, with renal failure seen in only 25—30% of patients with IgA nephropathy over 20—25 years.
- Risk factors for the loss of renal function include
  - the presence of hypertension or proteinuria
    - persistent proteinuria for ≥ 6 months has poor prognosis
  - the absence of episodes of macroscopic hematuria
    - male sex
    - older age of onset, and
    - extensive glomerulosclerosis or interstitial fibrosis on renal biopsy.

Management

- There is no agreement on optimal treatment.
- Some suggestions include
  - ACE inhibitors
  - steroid treatment or other immunosuppressive therapy in patients with persistent proteinuria after ACE inhibitor therapy
  - Tonsillectomy
  - Fish oil
  - When presenting as RPGN, steroids, cytotoxic agents, and plasmapheresis.

Chapter 13; Leishmaniasis (ካላዛር/ጓቋ/ እና ቁንጭር)

Dr. Mulualem. G, Dr. Robel. D

Clinical features and how to write hx of VL patient

History

The approach we discussed here is about Visceral leishmaniasis/VL/. Other forms of leishmaniasis such as cutaneous leishmaniasis are discussed in the discussion part only.

- *VL case definition* → N.B case definition is very important in case of epidemics
  "A person who presents with fever for more than 2 weeks and an enlarged , spleen (splenomegaly) and/or enlarged lymph nodes (lymphadenopathy), or , either loss of weight, anemia or leucopenia while living in a known VL endemic area or having travelled to an endemic area".
- Visceral Leishmaniasis should always be suspected when an individual presents with prolonged fever from the endemic areas.
- The Diagnosis of VL relies on clinical, serological, parasitological and molecular findings.
- The definitive diagnosis is demonstration of the parasite in a tissue aspirate.

Clinical Diagnosis

- Clinical signs and symptoms associated with VL include fever for more than two weeks, fatigue, weakness, loss of appetite, weight loss, malaise, cough, diarrhea, epistaxis, cachexia, abdominal pain, anemia, pancytopenia, and, associated with parasitic invasion of blood and reticulo-endothelial system, enlargement of lymph nodes, spleen, and liver.
- Some of these clinical signs and symptoms are similar to other diseases prevalent in the areas where VL is endemic.
- The clinical diagnosis of VL is therefore based on the standard case definition of visceral Leishmaniasis, as given above
- Symptoms often persist for several weeks to months before patients seek medical care or die from the bacterial co-infection, massive bleeding or severe anemia.

Characterization of patient history

- Pt's may present with (i.e the chief compliant maybe;)

    - Fever
    - Abdominal Swelling over the LUQ (ንቃ)
    - Anaemia features
- Fever
    - Chronic fever lasting for ≥ 2 weeks
    - Gradual in onset
    - High grade and intermittent / sometimes Low grade and continuous
    - Associated with chills and rigor
    - Peak in the afternoon and night, relieved in the morning
        - ✓ Usually double or triple onset daily
- Swelling over the LUQ of abdomen
    - Painless
    - Starts from the LUQ and grows towards the umbilicus (mid abdomen) which increase in size progressively to involve the whole abdomen with in ''X'' days
    - Associated with
        - ✓ Dragging sensation and feeling of abdominal fullness
        - ✓ Early satiety
        - ✓ Anorexia, vomiting and weight loss
    - How many days after the onset of fever, does the swelling begins? → e.g. pt noticed the swelling 2 weeks after the onset of fever
- Easy fatigability (weakness)
    - From supra ordinary to sub ordinary activity through time to the extent s/he unable to perform his/her daily activities
- Anaemia smx's
- Weight loss
- If s/he Lives in kalazar and malaria endemic area *(RF)*
        - ✓ Or travel hx to endemic area (when, how long s/he stayed there)
        - ✓ Similar illness in the vicinity
        - ✓ Malarial attack (how many times is the recurrence; last malarial attack is ''X'' months back) *(→ chronic CXN of malaria/HMS/ is DDX for VL)*

N.B

weight loss despite increased appetite in

- Kalazar
- DM
- Thyrotoxicosis
- Malabsorption

What is the difference between abdominal swelling and abdominal distension?

- **Abdominal distension** occurs when gas (air) or fluid accumulates in the abdomen causing its outward expansion beyond the normal girth of the stomach. Underlying causes include ascites, Intestinal obstruction etc.
- The term **Abdominal swelling** is used when there is intraabdominal organ enlargement causing increased abdominal girth (e.g. hepatosplenomegaly) or mass arising from the abdomen

- The clinical manifestations of the disease are caused by multiple factors. The most common causes are mainly due to:
  - Splenomegaly resulting in
    - Sequestration of blood
    - Pressure effect of massive spleen
  - Pancytopenia resulting in
    - Low hemoglobin
    - Low WBC → low immunity and high incidence of infections
    - Low platelets → bleeding

Risk factors *(especially to be infected by sand flies)*

- ✓ Some of the **factors found to be associated with the spread** include;
  - Living in endemic area or travel history to endemic area (living in lowland area and forest)
  - Poor socioeconomic status (poverty and malnutrition) associated with presence of the sand fly vector and reservoirs.
  - Male gender → engaged in outside activity (sleeping outside the house during farming)
  - Occupation → farmer
- ✓ Immunocompromisation
  - *Leishmania*/HIV co-infection is an important factor for the spread of the disease
- ✓ Age → youngsters have acute manifestation

Complication of VL

- **2ry infection**
  - The infection of the lymphoid tissue results in **suppression of the immune response** which is a predisposition for other infections.
  - commonly encountered infections include;
    - Ear infection (e.g. Otitis media)
    - Pneumonia
    - TB (2ry TB infection is common in VL patients)
    - GI infection (gastroenteritis, dysentery, diarrhea)
      - Diarrhea and cough can occur due to mucosal involvement of the gastro-intestinal and respiratory tract.
    - sepsis
      - for VL patients, Signs of bacterial co-infection should be ruled out because bacterial pneumonia and gastro-intestinal infections are common.
- Anaemia → 2ry to
  - Hypersplenism
  - Haemolysis
  - Bleeding
  - Short life span of RBC
  - Ineffective erythropoiesis → due to infiltration of BM by parasite
    - All cell lines are often affected causing pancytopenia
- **Bleeding**
  - Due to pancytopenia or post SSG treatment
- In Patients with an advanced stage of the disease;
  - Cachexia and edematous from hypoalbuminemia or CHF due to the anemia.
  - Hepatic dysfunction, jaundice and ascites can also occur.
  - Chronic diarrhea, malabsorption → rarely due to invasion of the intestine by parasite
- Malnutrition
  - Over 1/3rd of VL patients present with moderate to severe state of malnutrition which further predisposes them to infections and affects the prognosis of VL treatment.
- **PKDL** (post kalazar dermal leshmaniasis)
  - Chronic skin rash (erythematous macule, plaque and nodule) following clinical response to VL treatment

N.B
Common cause of death in VL are bleeding, severe anemia and 2ry infection

Sample history

Chief compliant

fever of 2 months duration

HPI

This patient was last relatively healthy two months back, at which time he began to experience insidious onset of low-grade intermittent fever sometimes high grade especially in the afternoon and night. for such compliant he visited a nearby clinic and was given a white circular tablet to be taken twice a day and unspecified injection but no improvement.

A month after the onset of fever he noticed a painless abdominal swelling which begins over the LUQ of abdomen and grows towards the umbilicus (mid abdomen) then increase in size progressively to involve the whole abdomen within three weeks duration associated with dragging sensation and feeling of abdominal fullness, early satiety, anorexia and unquantified but significant weight loss to the extent his trousers become loose.

Two weeks before admission he started to experience easy fatigability to the extent that he couldn't be able to perform his routine daily activities associated with blurring of vision, palpitation and light headedness but no tinnitus, vertigo, dyspnea, orthopnea or PND.

For this he visited quara primary hospital where unspecified blood tests were done, transfused with one bag of blood and he was told that he may have kalazar ("guaqua") and referred to our leishmaniasis center for confirmation and better management.

- He lives in kalazar and malaria endemic area and there is similar illness in the vicinity. He had Hx of repeated malaria attack. His last attack was 2yrs back where he was treated and got relieved. But he has no hx of kalazar attack
- No hx of HTN, DM or asthma *(immunocompromisation → RF)*
- No hx of nasal bleeding, gum bleeding, melena or haematochezia *(bleeding disorder → CXN)*
- No hx of abdominal pain, diarrhoea or vomiting *(gastroenteritis, dysentery → CXN)*
- No hx of yellowish discoloration of the eyes, RUQ abdominal pain, itching sensation, stool or urine colour change *(cirrhosis→ CXN or amoebic liver abscess → DDX)*
- No hx of river water contact or post river water contact itching *(schistosomiasis/HSS/ → DDX)*

- No hx of bone pain, nasal bleeding, pesticide/herbicide exposure, chemoradiotherapy, swelling over the neck, axilla or groin *(haematologic malignancy/CML, NHL/ → DDX)*
- No hx of chronic cough, contact with chronic cougher or previous TB treatment *(Disseminated TB to spleen → DDX)*
- No hx of sore throat, reddish discoloration of urine, dental/oral manipulation, IV drug abuse or intracardiac device *(SBE/subacute bacterial endocarditis/→ DDX)*
- No hx of malar rash, photo sensitivity or joint pain *(SLE → DDX)*
- No hx of raw milk drinking or participation in cattle delivery *(brucellosis → DDX)*

Finally, he was admitted to our hospital walking by himself

Physical examination (pertinent findings)

1 GA

- Cachexia (in advanced VL)
- Ashen Gray appearance (darkening of face)
    - The term ''*kala-azar''*, from Hindu for "black fever", may be related to this clinical feature

2 Vital signs

- Febrile
- Tachycardia and bounding pulse → sign of high output failure (CHF) in response to anaemia

3 HEENT

- Pale conjunctiva → anaemia
- Active nasal bleeding or clotted blood over the nostrils → bleeding 2ry to thrombocytopenia
- Ear discharge, sinusitis → 2ry infection
- Subconjunctival haemorrhage → IE, VL
- Jaundice → haemolytic anaemia

4 LGS

- LAP → VL, NHL/HL, Other malignancies

5 RS

6 CVS

- CHF 2ry to severe anaemia → S_3 gallop, raised JVP, ESM (ejection systolic murmur)
- Valvular lesion due to IE

7 Abdominal examination

- HSM (Hepatosplenomegaly) ± (LAP, per splenitis)
  - ✓ Non tender (rarely tender due to capsular pressure)
  - ✓ Soft
  - ✓ Firm in consistency
  - ✓ Smooth surface
  - ✓ Massive splenomegaly
  - The accumulation of infected mononuclear phagocytic cells in the spleen and the kupfer cells in the liver result in the hypertrophy of the organs to a clinical apparent hepatosplenomegaly.

8 GUS

9 MSS

- Oedema → advanced kalazar, lymphoma, CHF 2ry to severe anaemia
- Spine tenderness → NHL

10 IS

- Pallor → anaemia
- Dry, scaly skin (sometimes diffuse, warty, non-ulcerated skin lesion)
- Purpura, petechiae → bleeding tendency
- Hyperpigmentation and ashen Gray appearance

11 NS

DDX

1. Lymphoma (NHL)

- Extra nodal involvement of lymphoma includes **BM (DDX for VL),** thyroid, lung, brain, skin, testes
- LAP→ painless, discrete, firm
- HSM
- Fever, weight loss, night sweat, easy fatigability
- Bone pain
- Paraplegia

N.B

Lymphoma can be classified as

- Very aggressive
  - ✓ Burkitt lymphoma
  - ✓ ALL (Acute lymphoblastic leukemia)
  - ✓ Oncologic emergencies
- Aggressive
  - ✓ Mantle cell lymphoma
  - ✓ DLBCL (diffuse large B cell lymphoma)
- Indolent

2. Leukaemia (CML)

- These patients have fever, malaise, bleeding tendencies, weight loss and splenomegaly.
- They are also susceptible to other infections.
- Blood tests in the laboratory show a high white blood cell count.
- Phases of CML include;
  - a) Chronic phase (<10 % blast cells)
    - ✓ Low grade fever, night sweat, fatigue
    - ✓ Bone pain due to infiltration by malignant cells
    - ✓ HSM
    - ✓ Leucocytosis (hyper viscosity SXX) sensitive to treatment
  - b) Accelerated phase (10 - 20 % blast cells)
    - ✓ Fever without infection
    - ✓ Bone pain
    - ✓ Splenomegaly
  - c) Blast crisis (>10 % blast cells)
    - ✓ Have acute leukaemia manifestations (AML→ 80%, ALL → 20%)
    - ✓ BM failure → bleeding, infection
    - ✓ Resistant to treatment

3. Malignancy in general → FUO

N.B FUO (fever of unknown origin caused by)

- Malignancy
- TB
- Intra-abdominal abscess
- CTD (connective tissue disorders)

4. MPD (myeloproliferative disorders)

5. SBE (IE)

- Sub-acute (2 - 3 weeks)
- RF include → dental/oral manipulation, IV drug abuse, intracardiac device
- Manifest with → sore throat, reddish discoloration of urine (haematuria), abnormal body movement, fever, **tipped splenomegaly**

6. Malaria

- Symptoms of acute malaria generally stays for few days, whereas symptoms of VL tend to be chronic.
- However, repeated attacks of malaria can cause chronic malaria that manifests itself with fever, severe anemia, splenomegaly, loss of weight and other constitutional symptoms that looks like VL.
- Treatment for malaria improves the patient situation. If no improvement VL may be considered.

7. HMS (**Hyperactive malarial Splenomegaly**) or **Hyperactive Tropical Splenomegaly**

- Tropical splenomegaly can also occur in the setting of chronic malaria.
- It is an immunological reaction to malaria.
- The patients may have had **massive splenomegaly (often combined with Hepatomegaly**) for years.
- There is **no fever.**
- It is a **diagnosis by exclusion** of other differentials for patients from malaria-endemic areas with a huge spleen.
- refer chronic CXN of malaria under short case of Nitsibin (click here → Malaria (ወባ))

8. Disseminated TB to spleen

- The patients will present with malnutrition and a history of fever and other constitutional symptoms of TB for several months.
- They may have an enlarged spleen (**tipped splenomegaly**) or lymph nodes as in miliary Tuberculosis.

9. HSS

- The patients can have a very large liver and spleen, which they have often had for a very long time.
- Patients may not have fever but can present with ascites and other portal hypertension signs.
- Stool or urine analysis will show eggs of *Schistosoma*.
- **Refer from the following**
  - HSS from DDX of CLD under long case of Nitsbin (click here → Chapter 9; CLD/ Chronic liver disease/ (የጉበት በሽታ))

- "Intestinal Helminthic Infestations (የአንጀት ጥገኛ ተውሳክ ፣የአንጀት ትላትል) and blood flukes" section from Short case of Nitsibin (click here → Schistosomiasis (ቢሊሃርዚያ))

10. Splenic abscess

- Present with Fever, Left upper quadrant pain and Splenomegaly
    - These patients have **high grade fever and a very tender spleen.**
- Presentation frequently is delayed
- May have risk factors such as Immunosuppression (including HIV infection and chemotherapy), Trauma
- The diagnosis is confirmed by abdominal ultrasound or CT scan

11. **Amebic liver abscess**

- Patients usually present with one to two weeks of right upper quadrant pain and fever
- other symptoms may include sweating, malaise, weight loss, and anorexia

12. SLE

- Common source of FUO
- Present with photo sensitivity, malar rash, migratory joint pain, myalgia, arthralgia

13. Typhoid Fever

- The classic presentation includes high fever, malaise, diffuse abdominal pain, and constipation or diarrhea.
- Patients usually have a slow heart rate (bradycardia), and, in severe cases, can progress to impaired mental status (confusion) or other serious complications.

14. **Typhus** → Typhus is also an acute febrile illness characterized by an abrupt onset of fever, headache and a maculopapular or petechial rash.

15. **Brucellosis**

- rare, mis diagnosed as TB
- there is history of contact with animal abortus
- Patients have a long history of fever, small or moderate splenomegaly and an enlarged liver.
- Usually there is also involvement of the joints or bones that results in musculoskeletal pains and arthritis.

16. **HIV/AIDS**

- HIV damages the immune system so that the body of an infected person cannot properly fight against diseases.
- Patients often suffer from recurrent diarrhoea, which may lead to malnutrition/wasting and dehydration, as in a *kala azar* patient.

17. IM (infectious mononucleosis)

IX

Investigations to be done for VL patient include;

- Leishmanial diagnostic investigations (see the algorithm below)
  - Parasite detection from Aspiration
  - Antibody detection
  - Antigen detection
  - Molecular techniques
- Other non-Leishmanial tests

1. Aspiration

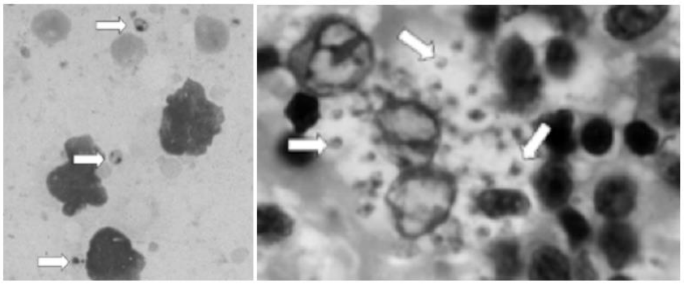
- Gold standard diagnostic IX modality
- Amastigotes (ovoid body) seen from the aspirate
  - **As discussed above, The Diagnosis of VL relies on clinical, serological, parasitological and molecular findings.**
  - Definitive diagnosis of VL is made by visualization of the amastigote form of the parasite by microscopic examination of aspirates from lymph nodes, bone marrow or spleen aspiration.
- RK39, LD body from PM and kalazar latex agglutination test confirmed by aspiration
- Used for VL or hematologic malignancy DX (mainly for leukaemia, lymphoma staging /BM involvement/)
- This diagnosis has **a high specificity** but the sensitivity of the microscopy varies for VL Dx

Organs to be aspirated for VL	sensitivity
1. Spleen	≥ 95% (93 — 99%)
2. BM	70% (53-86%)
3. LN	58% (53-65%)

- However, this is an invasive procedure which requires a hospital setting with blood transfusion service and experienced clinicians for the procedure. Thus, it may not always be applicable especially in remote regions where VL is endemic.
- Refer splenic, BM and LN aspiration from short case of Nitsbin (click here → Splenic Aspiration , BM aspiration, LN aspiration)

- After aspiration sample can be used for microscope smear evaluation or Culture in NNN media

a. Microscopic smear evaluation



Free amastigotes Intra-cellular amastigotes

Pictures (National malaria guideline 2nd edition); **Identification of the Leishmania parasite**; Leishmania amastigotes are oval or round and are usually seen in the cytoplasm of monocytes. Free parasites may be seen if the host cells are ruptured during preparation of the film.

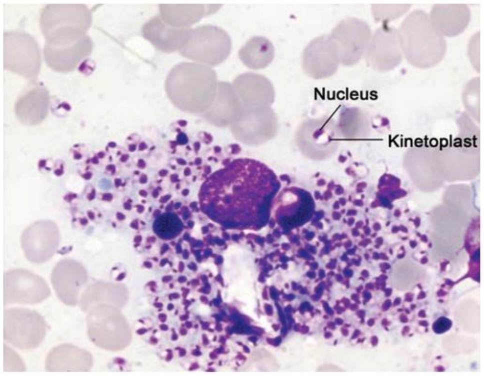


FIGURE 221-1(Harrison 20th edition); **A macrophage with numerous intracellular amastigotes** (2 - 4 μm) in a Giemsa-stained splenic smear from a patient with visceral leishmaniasis. Each amastigote contains a nucleus and a characteristic kinetoplast consisting of multiple copies of mitochondrial DNA. A few extracellular parasites are also visible.

- Leishmania amastigotes seen and indicate the grade. Examine at least 1000 fields before declaring a film to be negative.
- The average amastigote density is graded as follows;
    - **6+**: > 100 parasites per field (viewed with a 10× eyepiece and 100× oil-immersion lens)
    - **5+**: 10 - 100 parasites per field
    - **4+**: 1 - 10 parasites per field
    - **3+**: 1 - 10 parasites per 10 fields
    - **2+**: 1 - 10 parasites per 100 fields
    - **1+**: 1 - 10 parasites per 1000 fields
    - **0**: 0 parasite per 1000 fields

b. Culture in NNN (Novy-mcNeal-Nicolle) media

- Promastigote grows within 4 weeks after inoculation
- This technique remains restricted to referral hospitals or research centers.

2. Antibody Detection

- Immunodiagnostic techniques, which have been extensively used for the diagnosis of VL include;
    - Enzyme-linked immunosorbent assay (ELISA)
    - Immunofluorescent antibody test (IFAT)
    - Freeze-dried direct agglutination test (FD-DAT) or aqueous antigen direct agglutination test (AQ-DAT)
    - Fast Agglutination Screening Test (FAST)
    - Indirect hemagglutination test (IHA)
    - rK39 immunochromatographic (rk39-ICT) strip test and
    - rK39 ELISA
- However, all of these tests have **two major limitations**;
    - First, **they do not distinguish between present and past infections**, as the serum antibody level remains high after successful treatment. **Detection of relapse is not possible** with these methods.
    - Second, all these tests **fail to differentiate between symptomatic and asymptomatic infections**.
    - As a consequence, a significant proportion of healthy individuals in the endemic area with no history of VL are positive for anti-Leishmanial antibodies.
- The performance of the various serological tests in the diagnosis of VL is found to be
  good to excellent; **their sensitivity and specificity is ranging from 70 to 100%.**
- However, the facilitation of some of these tests (ELISA, IFAT, IHA) in the field where the disease is prevalent is limited because they need well-equipped laboratory and skilled personnel.
- Of all these tests, **DAT and rK39 have been extensively evaluated and used for the diagnosis of VL in the field and in laboratory settings**.

rK39 (recombinant kinase 39) strip test

- Common and available in Ethiopia.
- Serologic (antibody strip) test for VL
- Have 72% to 94 % sensitivity and 67 % to 98 % specificity
    - ✓ **More Specific and sensitive** (reach up to 99%) **in non-endemic** area like south east Asia (India)
    - ✓ **Not specific in endemic area like east Africa (Ethiopia, Sudan, Kenya)**
- Used for **screening purpose**
- For more refer ''Common Laboratory Investigations with practical points and procedures'' from Short case of Nitsibin (click here → **rk- 39 Rapid Diagnostic Test**)

DAT (direct agglutination test)

  - Has 95% sensitivity and 72 % to 93 % specificity
  - Anti-leishmanial titre (IgG)
  - **DAT** is a semi-quantitative test that uses V-shaped micro-titter plates in which increasing dilutions of patients' serum or blood are mixed with killed and stained freeze dried or aqueous *Leishmania donovani* promastigotes.
  - If specific antibodies are present agglutination will be visible within 18 hours

3. **Antigen Detection Test**

- The antigen detection test is **an ideal test because it is more specific than the antibody-based immunodiagnostic test.**
- It **helps to distinguish active from past infections.**
- This method is also useful in cases with a deficient antibody production, as in AIDS patients.
- **A urine latex agglutination (KATEX)** that detects heat-stable, low molecular weight carbohydrate antigen in the urine of VL patients has been developed.
- The evaluation of the performance of KATEX at the Indian subcontinent and East Africa has shown that this test has a **good specificity** but only a **low to moderate sensitivity**.

4. Leishmania skin test (Montenegro skin test)

- Intra dermal inoculation of leishmania (i.e. whole or killed promastigote)
- +ve test; if there is induration/erythema ≥ 5mm within 48 - 72 hr's of inoculation
- +ve after 2 - 24 months of infection

5. PM (peripheral morphology)

- LD (leishmania donovani) body → amastigote seen by microscopy
- PM also important for hematologic malignancy (e.g. full of neutrophil in CML

6. CBC

- Anaemia or pancytopenia
- Hyper gamma albuminemia (activation of poly clonal B cells)
- Eosinophilia (reactive lymphocytosis/monocytosis)

7. Coagulation profile

8. PICT

- Screen all VL pt for RVI and Treat VL 1st then initiate ART. If not, they will develop IRIS
- For mgt purpose (e.g Ambisome is used in RVI - VL treatment)

9. OFT

- LFT and Liver enzymes
- RFT → amphotericin B, SSG and paromomycin are nephrotoxic

10. ECG, CXR, ECHO

- Done as baseline and follow up

- ECG for SSG treatment CXN (arrythmia)
- CXR for 2ry infection like TB, Pneumonia (2ry TB infection is cmn in VL patients)

11. Molecular Techniques

- Compared to the other diagnostic techniques available, the molecular approaches remain **expensive and technically highly demanding**. Their **applicability in the endemic areas is highly questionable (in our setup to costly not applicable).**
- molecular methods for Leishmaniasis diagnosis include
    - pulsed-field gel electrophoresis
    - multilocus enzyme electrophoresis and
    - PCR-based assay

PCR-based assay

- PCR based assays currently constitute the main molecular diagnostic approach of Leishmaniasis.
- The major importance of is its high sensitivity and specificity (up to 100%) irrespective of the species or genus.
- Second, the burden of infection could be assessed by PCR. This may be highly relevant in monitoring disease progression and outcome of an anti-Leishmanial therapy.
- Third, the viability of detected parasites could be demonstrated by other forms of nucleic acid-based techniques, reverse transcription real time PCR (which is expensive), or less expensive protocol quantitative nucleic acid sequence-based amplification [QT-NASBA].
- Fourth, Leishmania species and strain identification can be performed by a series of PCR-based assays. This is useful for the clinical management due to the link between Leishmania species, and disease severity and treatment outcome.
- Finally, a molecular diagnosis might allow defining parasite-specific features, such as virulence and drug resistance, and so-called parasite tracking, if highly discriminatory fingerprinting tools are employed. However, PCR-based protocols need standardization and optimization.

12. Animal inoculation

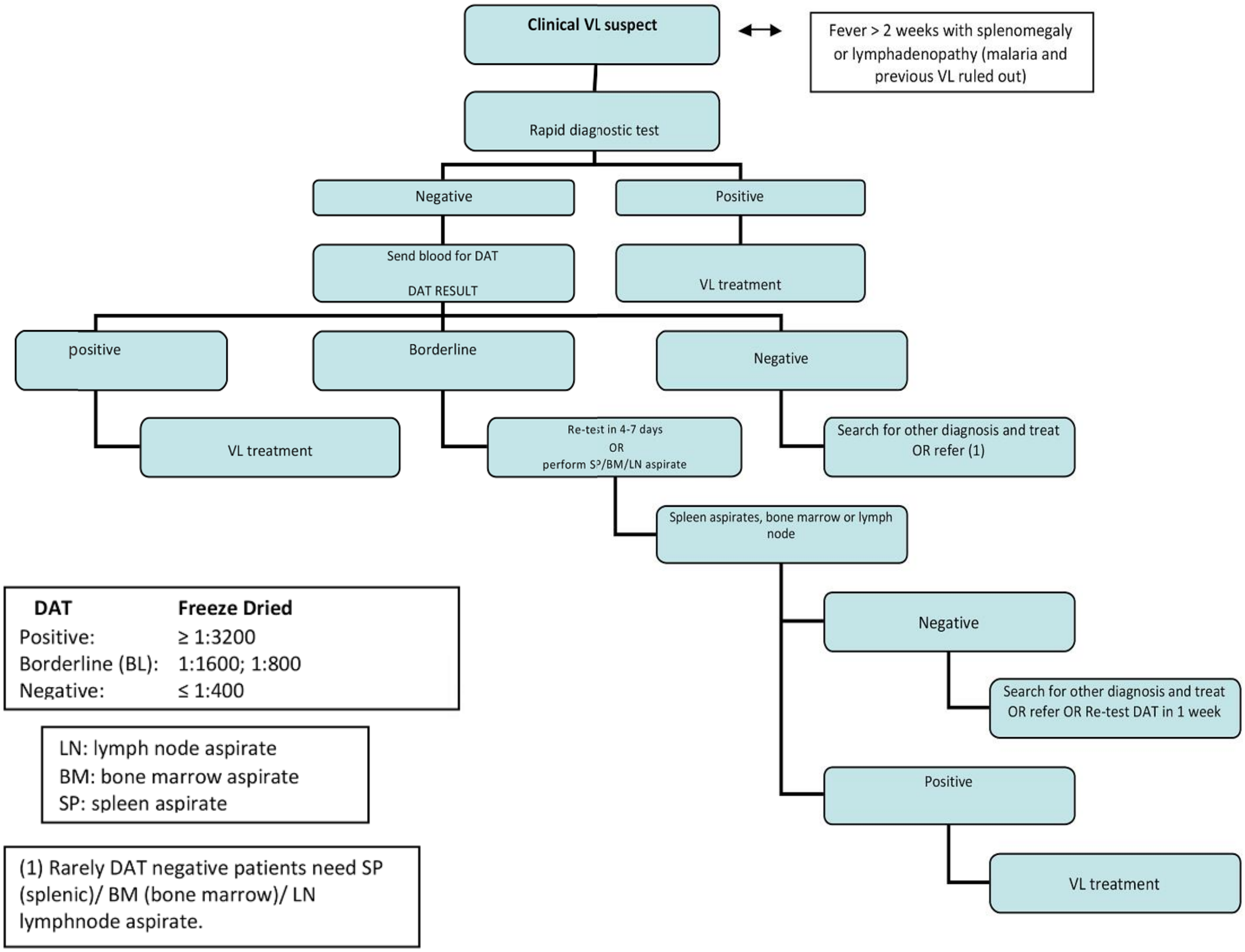
- Inoculate by infected specimen
- Then examine the animal for sign of infection

13. Chromosomal study

- ✓ Philadelphia chromosome of CML
- ✓ So, for CML do chromosomal study *(not available in our setup)* and PM

Tip→ from the above list those written in **bold and blue** letter commonly done in our set up

Diagnosis Algorithm for VL in Ethiopia


Clinical VL suspect
Fever > 2 weeks with splenomegaly or lymphadenopathy (malaria and previous VL ruled out)
Rapid diagnostic test
Negative
Positive
Send blood for DAT
DAT RESULT
VL treatment
positive
Borderline
Negative
VL treatment
Re-test in 4-7 days
OR
perform SP/BM/LN aspirate
Search for other diagnosis and treat OR refer (1)
Spleen aspirates, bone marrow or lymph node
Negative
Search for other diagnosis and treat OR refer OR Re-test DAT in 1 week
Positive
VL treatment

DAT	**Freeze Dried**
Positive:	≥ 1:3200
Borderline (BL):	1:1600; 1:800
Negative:	≤ 1:400

LN: lymph node aspirate
BM: bone marrow aspirate
SP: spleen aspirate

(1) Rarely DAT negative patients need SP (splenic)/ BM (bone marrow)/ LN lymphnode aspirate.

Figure: Diagnosis Algorithm for VL in Ethiopia

Discussion

13.1 Leishmaniasis

- Leishmaniasis is a vector-borne disease caused by protozoan parasite of the genus Leishmania.
- It is transmitted by the vector *phlebotomine* sand fly.
- Some of the Leishmania species known to cause disease in humans are:
    - *L. donovani* species complex (including *L. donovani* and *L. infantum/chagasi*)
    - *L. major*
    - *L. tropica*
    - *L. aethiopica,*
    - *L. braziliensis* and
    - *L. mexicana* species complex.

Epidemiology

- The disease is endemic in environments that range from deserts to rain forests in rural and urban settings in over 98 countries of the tropics, subtropics, and southern Europe.
- Estimations of the burden caused by the Leishmaniasis disease in the world is challenging.

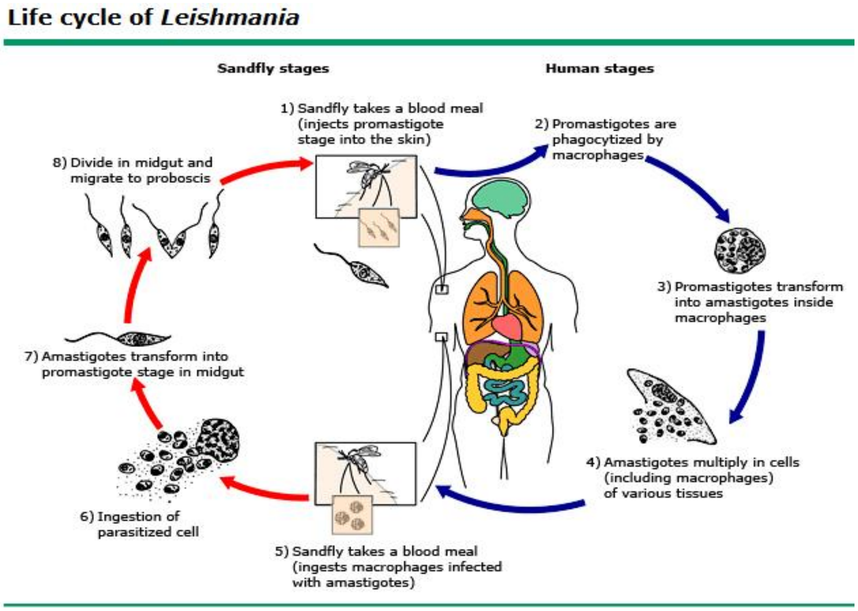
Leishmaniasis burden In Ethiopia

- In Ethiopia, cutaneous leishmania (CL) is distributed mainly in the highlands on an elevation between 1,400 - 3,175 meters above sea level.
- According to the 2012 WHO global Leishmaniasis estimate**, Ethiopia is one of the 10 high burden countries for CL.**
- VL is predominantly found in the lowlands with varying degrees of endemicity.
- It is estimated that the annual burden of VL ranges from 2,000 to 4,500 cases.
- The **endemicity of VL** was recently extended to at least five administrative regions, namely, **Amhara, Tigray, SNNPR, Oromia and Somali.** In addition, there have been recent outbreaks in northern and southern parts of the country: **Libo Kemkem Woreda in Amhara region**, **T/Adiabo Woreda in Tigray region** and **Imey in Somali region.**

Life cycle of Leishmania

- Leishmania parasites are digenetic parasites that **need two hosts**, the **sandfly and a mammalian host**, to complete their life cycle (see picture below).
- **Over 20 Leishmania species** are **pathogenic to humans** and 30 sandfly species are proven in the vectors.
- There are two ways of transmission of Leishmaniasis. These are;
    - **Zoonotic** → which includes animal reservoir hosts, mainly dogs, in the transmission cycle, or

  - **Anthroponotic →** in which humans are the sole source of infection for the vector.
- Moreover, different species of phlebotomine sandflies need different habitats to survive and have different biting preferences (in/outdoor, forest/ village, day/night). This has consequences for the transmission of the disease and control measures to be applied.
- **VL in Ethiopia is caused by *L. donovani* with an anthroponotic transmission.**


Life cycle of Leishmania
Sandfly stages
Human stages
1) Sandfly takes a blood meal (injects promastigote stage into the skin)
2) Promastigotes are phagocytized by macrophages
3) Promastigotes transform into amastigotes inside macrophages
4) Amastigotes multiply in cells (including macrophages) of various tissues
5) Sandfly takes a blood meal (ingests macrophages infected with amastigotes)
6) Ingestion of parasitized cell
7) Amastigotes transform into promastigote stage in midgut
8) Divide in midgut and migrate to proboscis

Picture; Life cycle of *Leishmania;* Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies. The sandfly injects the infective stage (ie, promastigotes) from its proboscis during blood meals **(1)**. Promastigotes that reach the puncture wound are phagocytized by macrophages and other types of mononuclear phagocytic cells **(2)**. In these cells, progmastigotes transform into the tissue stage of the parasite (ie, amastigotes) **(3)**, which multiply by simple division and proceed to infect other mononuclear phagocytic cells **(4)**. Parasite, host, and other factors affect whether the infection becomes symptomatic and whether cutaneous or visceral leishmaniasis results. Sandflies become infected by ingesting infected cells during blood meals **(5,6)**. In sandflies, amastigotes transform into promastigotes, develop in the gut (in the hindgut for leishmanial organisms in the *Viannia* subgenus; in the midgut for organisms in the *Leishmania* subgenus) **(7)** and migrate to the proboscis **(8)**.

Table; Leishmania Parasite, Their significance and Vectors			
	In Ethiopia		
Old/new world	Parasite	Significance	Vectors
Old world	L. aethiopica	Cutaneous leishmaniasis (CL), Diffuse cutaneous leishmaniasis (DCL), Mucocutaneous leishmaniasis (MCL)	P. longipes P. pedifer P. sergenti
	L. tropica	Cutaneous leishmaniasis (CL)	P. sergenti P. saevus
	L. major		P. duboscqi
New world	**L. donovani**	Visceral leishmaniasis (VL)	P. martini, P. Celiae

			P. orientalis
All over the world			
Old world	L. aethiopica L. tropica L. major	Cutaneous leishmaniasis (CL)	
New world	L. panamensis L. guyanensis L. peruviana L.mexicana L. brazilliensis		
Old world	L. aethiopica	Mucocutaneous leishmaniasis (MCL)	
new world	L. panamensis L. guyanensis L. brazilliensis		
Old world	L. aethiopica	Diffuse cutaneous leishmaniasis (DCL)	
new world	L. amzonensis L.mexicana		
Old world	L. donovani	Visceral leishmaniasis (VL)	
old & new world	L. Infantum		
new world	L. Chagasi		

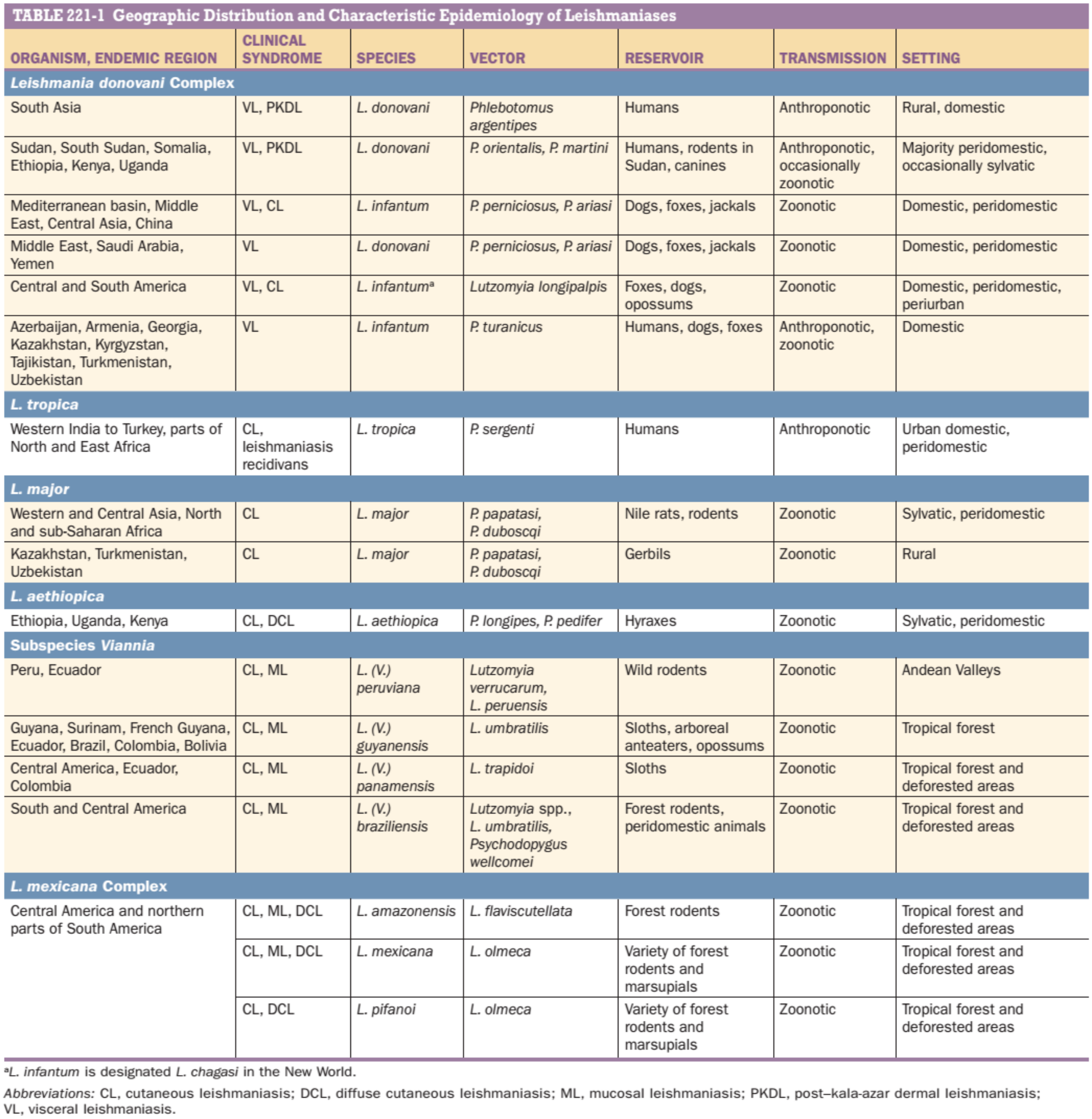


TABLE 221-1 Geographic Distribution and Characteristic Epidemiology of Leishmaniases

ORGANISM, ENDEMIC REGION	CLINICAL SYNDROME	SPECIES	VECTOR	RESERVOIR	TRANSMISSION	SETTING
***Leishmania donovani* Complex**						
South Asia	VL, PKDL	*L. donovani*	*Phlebotomus argentipes*	Humans	Anthroponotic	Rural, domestic
Sudan, South Sudan, Somalia, Ethiopia, Kenya, Uganda	VL, PKDL	*L. donovani*	*P. orientalis, P. martini*	Humans, rodents in Sudan, canines	Anthroponotic, occasionally zoonotic	Majority peridomestic, occasionally sylvatic
Mediterranean basin, Middle East, Central Asia, China	VL, CL	*L. infantum*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Middle East, Saudi Arabia, Yemen	VL	*L. donovani*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Central and South America	VL, CL	*L. infantum*[a]	*Lutzomyia longipalpis*	Foxes, dogs, opossums	Zoonotic	Domestic, peridomestic, periurban
Azerbaijan, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan	VL	*L. infantum*	*P. turanicus*	Humans, dogs, foxes	Anthroponotic, zoonotic	Domestic
L. tropica						
Western India to Turkey, parts of North and East Africa	CL, leishmaniasis recidivans	*L. tropica*	*P. sergenti*	Humans	Anthroponotic	Urban domestic, peridomestic
L. major						
Western and Central Asia, North and sub-Saharan Africa	CL	*L. major*	*P. papatasi, P. duboscqi*	Nile rats, rodents	Zoonotic	Sylvatic, peridomestic
Kazakhstan, Turkmenistan, Uzbekistan	CL	*L. major*	*P. papatasi, P. duboscqi*	Gerbils	Zoonotic	Rural
L. aethiopica						
Ethiopia, Uganda, Kenya	CL, DCL	*L. aethiopica*	*P. longipes, P. pedifer*	Hyraxes	Zoonotic	Sylvatic, peridomestic
Subspecies *Viannia*						
Peru, Ecuador	CL, ML	*L. (V.) peruviana*	*Lutzomyia verrucarum, L. peruensis*	Wild rodents	Zoonotic	Andean Valleys
Guyana, Surinam, French Guyana, Ecuador, Brazil, Colombia, Bolivia	CL, ML	*L. (V.) guyanensis*	*L. umbratilis*	Sloths, arboreal anteaters, opossums	Zoonotic	Tropical forest
Central America, Ecuador, Colombia	CL, ML	*L. (V.) panamensis*	*L. trapidoi*	Sloths	Zoonotic	Tropical forest and deforested areas
South and Central America	CL, ML	*L. (V.) braziliensis*	*Lutzomyia* spp., *L. umbratilis, Psychodopygus wellcomei*	Forest rodents, peridomestic animals	Zoonotic	Tropical forest and deforested areas
***L. mexicana* Complex**						
Central America and northern parts of South America	CL, ML, DCL	*L. amazonensis*	*L. flaviscutellata*	Forest rodents	Zoonotic	Tropical forest and deforested areas
	CL, ML, DCL	*L. mexicana*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	Tropical forest and deforested areas
	CL, DCL	*L. pifanoi*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	Tropical forest and deforested areas

[a] *L. infantum* is designated *L. chagasi* in the New World.

Abbreviations: CL, cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; ML, mucosal leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

- **The clinical forms range from** the self-healing **localized cutaneous form (LCL)** to the more complicated non-self-limiting **mucocutaneous form (MCL)** and **diffused cutaneous (DCL)** forms to the potentially fatal **visceral form (VL,** also called *kala-azar*).

13.2 VL; Visceral Leishmaniasis/*kala-azar*/ (ካላዛር ፣ ጓቄ)

- VL (also known as *kala-azar*, a Hindi term meaning "black fever") is is the severe form of the disease, caused by the *Leishmania donovani* complex, which includes *L. donovani* and *Leishmania infantum* (the latter designated *Leishmania chagasi* in the New World); these species are responsible for anthroponotic and zoonotic transmission, respectively.

- **India and neighboring Bangladesh, Sudan and neighboring South Sudan, Ethiopia, and Brazil are the four largest foci of VL and account for 90% of the world's VL burden.**
- **VL in Ethiopia is caused by *L. donovani*** by an anthroponotic transmission.
- Most infections in immunocompetent individuals remain asymptomatic.
- The parasites replicate within the mononuclear phagocytic cells and disseminate throughout the reticulo-endothelial system when the immunity is weak.
- The incubation period typically ranges from 2—6 months, but it can also range from a few weeks to years.
- See clinical features from approach part above.

13.2.1 Management of VL

- The objectives of VL treatment are to:
  - Reduce the parasite burden
  - Prevent drug resistance
  - Avoid toxic drug effects, and
  - Improve the clinical condition of patients and to manage complications (anemia, malnutrition and secondary infections)

Supportive Management

- **Nutrition:**
  - VL patients require adequate nutrition, vitamin and micro-nutrient supplementation to speed up recovery, improve treatment response and decrease or avoid the risk of relapse.
  - Measure nutritional status with BMI or weight for height and follow the national nutrition guideline (national protocol) for management.
- **Management of Anemia:**
  - VL patients often present with **moderate to severe degree of anemia** due to bone marrow infiltration by the Leishmania parasite, hypersplenism, auto-immune reactions or bleeding.
  - **Epistaxis** could occur due to thrombocytopenia and mucosal infection. **If it is severe nasal packing and posterior epistaxis balloon might be required.**
  - **The anemia may require transfusion if severe.**

Pharmacologic management

First-Line Regimens for Primary VL

- The first-line drugs for the management of primary visceral Leishmaniasis in Ethiopia are a combination of **antimonials with aminiglycosides** and **Liposomal Amphotericin B for special situations** as described below.
  - Antimonials include Sodium Stibogluconate (generic SSG), and meglumine antimoniate (Glucantime).

  - The half-life of antimonials is about 2 hours and their elimination is through the kidneys.
  - SSG and Glucantime have similar mechanism of action, efficacy and side effects.
  - **Preparation;** Sodium Stibogluconate = 100mg/ml, Glucantime = 81mg/ml

Combination Therapy: Sodium Stibogluconate (SSG) and Paromomycin

- **sodium stibogluconate (20mg/kg /day), and paromomycin (15mg/kg /day), IM, daily for 17 days**
- The preferred choice for its better safety and affordability. And also efficacy of 90-94% in Ethiopia
- The efficacy of the combination therapy is similar to that of the pentavalent antimonials monotherapy, with the advantage of a decreased toxicity, shorter treatment duration and cheaper cost.
- Currently SSG and paromomycin can be administered at the same time but in two separate injections, i.e., one in either buttock or the PM injection in another IM area. Please, also note that the Paromomycin injection is a very small volume injection.
- Several studies in India have recently shown that three separate combinations demonstrate high cure rates. These have yet to be investigated in the Ethiopian context. These include;
  - liposomal amphotericin B (LAmB) plus miltefosine, or
  - LAmB plus Paromomycin, or
  - Miltefosine plus Paromomycin

B. Sodium Stibogluconate or Meglumin Antimoniate (Monotherapy)

- **SSG, 20mg/kg/day, IM or or by a slow IV infusion within 5 minutes., daily for 30 days**
- In the absence of or in case of stock ruptures of Paromomycin, Pentavalent antimonials can be used in monotherapy
- Consideration should be given in Leishmaniasis patients with edema to avoid overdosage.
- Weekly weight measurements need to be made and the dosage should be recalculated accordingly.

Precautions during the use of antimonials : These may require stoppage of the drug and a possible shift of treatment to AmBisome:

- Acute pancreatitis with abdominal pain and vomiting
- Jaundice developing while on treatment
- Elevated liver function tests (5 times of the normal value)
- Elevated creatinine level
- Evidence of cardio-toxicity
- Uninterrupted severe vomiting
- Declining hematologic parameters, and
- Failure to respond to treatment after two weeks of drug treatment

➢ VL Patients, who require a close follow-up during treatment with antimonials include, those with;

  - A very high or low age
  - Severe illness
  - Severe anemia
  - HIV co-infection or
  - Severe malnutrition
- Although resistance to antimonials is an issue in other countries, the response rate for SSG in Ethiopia is good currently especially for those who are not co-infected with HIV.

Liposomal Amphotericin B (LAmB, AmBisome)

- Liposomal Amphotericin B is the safest drug, it is also the most expensive one.
- It is the first-line treatment for VL in special situations. Hence, Liposomal Amphotericin B **is recommended in those patients with;**
  - Pregnancy → As the use of antimonials is not safe in pregnant women due to the higher risk of miscarriage, its use is not recommended where there is an alternative drug to use.
  - HIV-co-infection → this is because, the use of antimonials in *Leishmania*/HIV co-infected patients is found to be less effective with higher and frequent relapse rates and severe (fatal) toxicity.
  - Severe illness
  - Severe anemia
  - Severe malnutrition
  - Extremes of age (below 2 years or above 45 years).
  - In special situations with severe risk factors for death at the patient's admission, antimonials toxicity has proved to be very high and, therefore, LAmB is preferable if available for these patients.

Second-Line Treatment for Primary Visceral Leishmaniasis

- The second line treatment for VL in Ethiopia is **Liposomal Amphotericin.**
- Indications for the use of second-line VL treatment are;
  - Drug toxicity
  - Relapse
  - Treatment failure
  - Very severe illness
  - Pregnancy and
  - VL/HIV co-infection.

Liposomal Amphotericin B (AmBisome)

- **Dosage and Administration:**
  - AmBisome**, 5mg/kg/day over a period of 6 days** (i.e. 30mg/kg in total).
  - It is administered by reconstitution with 5% D/W; with a volume of 100ml of D/W for 50mg of AmBisome
    - AmBisome vials contain 50 mg/ml.

        - for 100mg or 2 vials of AmBisome 200ml of D/W, for 3 or more vials use all the 500ml D/W.
    - It is advised to use whole vials to avoid wastage but the drug should be discarded after 24 hours of reconstitution.
    - **The infusion can run over 30 to 60 minutes**
- Liposomal Amphotericin is a lipid formulation of Amphotericin B in which the drug is packaged with cholesterol and other phospholipids within a small unilamellar liposome.
- This **is an extremely safe and efficacious drug** for the treatment of visceral Leishmaniasis.
- ts main disadvantage is its high cost.

Miltefosine

This is **the only oral anti-leishmanial drug**

Taken at a dose of; **2-3mg/kg/day** (100mg/day for > 25kg) **for 28 days**.

Miltefosine is an alkyl phospholipid (hexadecacylphosfocholine), originally developed as an oral anticancer drug that has shown to have anti-leishmanial activity.

In one study in Ethiopia, Miltefosine was found to be less effective but safer than antimonials in HIV/VL co-infected patients.

Miltefosine is potentially **teratogenic** and, thus, it is **contraindicated during pregnancy**.

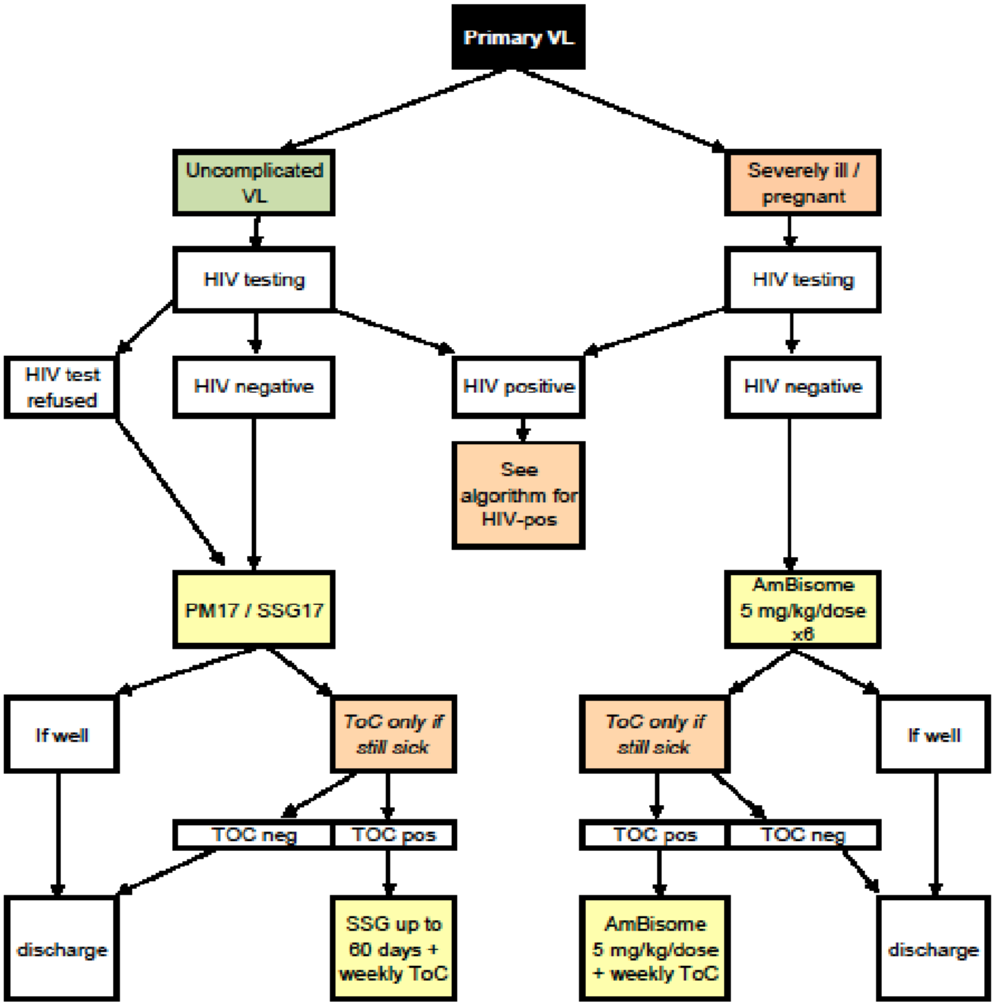
- Lactating women and women of childbearing age must use effective contraception during the treatment and for 3 months afterwards.

C) Paromomycin (Aminosidine)

- Paromomycin is an aminoglycoside antibiotic (Pharmacologic Category; Amebicide).
- **paromomycin (15mg/kg /day), IM.** The 15mg/kg sulphate is equivalent to 11mg/kg base, whereas 20mg/kg sulphate is equivalent to 16mg/kg base.

Primary VL treatment algorism

Visceral Leishmaniasis treatment algorithm: Primary VL, immunocompetent


Primary VL
Uncomplicated VL
Severely ill / pregnant
HIV testing
HIV testing
HIV test refused
HIV negative
HIV positive
HIV negative
See algorithm for HIV-pos
PM17 / SSG17
AmBisome 5 mg/kg/dose x6
If well
ToC only if still sick
ToC only if still sick
If well
TOC neg
TOC pos
TOC pos
TOC neg
discharge
SSG up to 60 days + weekly ToC
AmBisome 5 mg/kg/dose + weekly ToC
discharge

Note: Treatment of SSG can be extended to 60 days but with precaution in safety monitoring.

13.2.2 Patient Follow-Up in Management of VL

- Patient monitoring is vital during VL treatment as the currently used antileishmanial drugs are toxic.
- Hence, **patients should be invariably admitted** for visceral Leishmaniasis treatment, close monitoring of drug adverse effects, supportive management, and follow-up of patient's progress
- During treatment patients require a strict follow-up of their response to treatment and drug side effects.
- **Follow-up on clinical parameters** including
  - Fever
  - spleen size and
  - patient wellbeing is important.

- laboratory tests for follow up include;
    - a hematologic profile
    - chemistry
    - ECG
    - Radiography.
- Prevention and treatment of secondary infections, diagnosis and treatment of complications and nutritional supplementation are important during the treatment of visceral Leishmaniasis.
- At the end of therapy, the **outcome of the treatment** should be recorded based on the status of the patient as **discharged/improved, cured, treatment failure, relapse, referred or defaulted**.
- At discharge, the patient should be given regular **appointments 3 and 6 months after the treatment.**
- The patient should be advised to visit the health facility for recurrence of the clinical features and/or appearance of skin rash.

Evaluating Cure

- At the end of VL treatment, patients should be re-assessed for response clinically or using laboratory tests.

Clinical Response

- Many patients get worse during the first few days of treatment with SSG.
- After 7 to 10 days, patients become afebrile and begin to look stronger with increased alertness and appetite.
- By day 14, the spleen size regresses, the Hgb level rises and there is weight gain in the absence of edema.
- At the end of successful treatment, patients look improved, afebrile, and usually have a smaller spleen size than on admission and have an increased Hgb level.
- Look for signs of co-existing TB or HIV, both of them will increase the risk of treatment failure.
- *Cure* is best defined as the absence of clinical features of the disease after completion of the recommended dose and duration of treatment for VL in addition to a negative parasitological test for LD bodies.

Initial Parasitological Cure

- **Test of cure (TOC)** is performed at the end of treatment when there is no or insufficient clinical improvement and in treatment of relapse for decision to stop treatment.
- There is no clinical sign that best correlates with a positive test of cure or that predicts an increased risk of relapse.
- Clinical evaluation should get the priority over a test of cure for every patient under the currently available invasive procedures.
- TOC should be reserved for cases where response is in doubt, in the treatment of relapses and for monitoring emergence of drug resistance.
- In addition, TOC is done to assure that discharge is appropriate for patients who may have difficulty returning for follow-up.

- There must be 2 negative tests of cure (TOC) results before discharging patients with VL relapse.
- The tests are done one week apart to ensure that there is at least a week of treatment after the first negative TOC.
- The likelihood for a positive TOC after treating a relapse is higher than 10% and any further relapses will be more difficult to cure.
- In some situations, it is better to refer patients with VL relapse for treatment into a hospital setting.

Positive Parasitology (TOC) at the End of Treatment

- f the TOC is scanty positive, continue the same treatment until two consecutive weekly aspirates are negative.
- The limit of duration of therapy is 60 days for SSG and a total dose of 40mg/kg for AmBisome, if at this point the TOC is still positive, use a 2nd line treatment.
- *Non-response* is defined as failure to decrease the parasitological grade after adequate treatment.

Definitive Test of Cure

- It is not a routine practice to do TOC at the 6th month of patient follow-up if the patient does not fit for clinical visceral Leishmaniasis.
- **Relapse** is diagnosed when a patient with VL treatment history presents with clinical visceral Leishmaniasis and is diagnosed with **positive parasitology (LD bodies) after successful completion of the treatment.**
- **Re-infection** is possible for VL but most cases are considered as relapse and treated accordingly.
- Clinical judgement will always play the final role in any decision-making process given the variability of individual VL cases.

13.2.3 VL Relapse

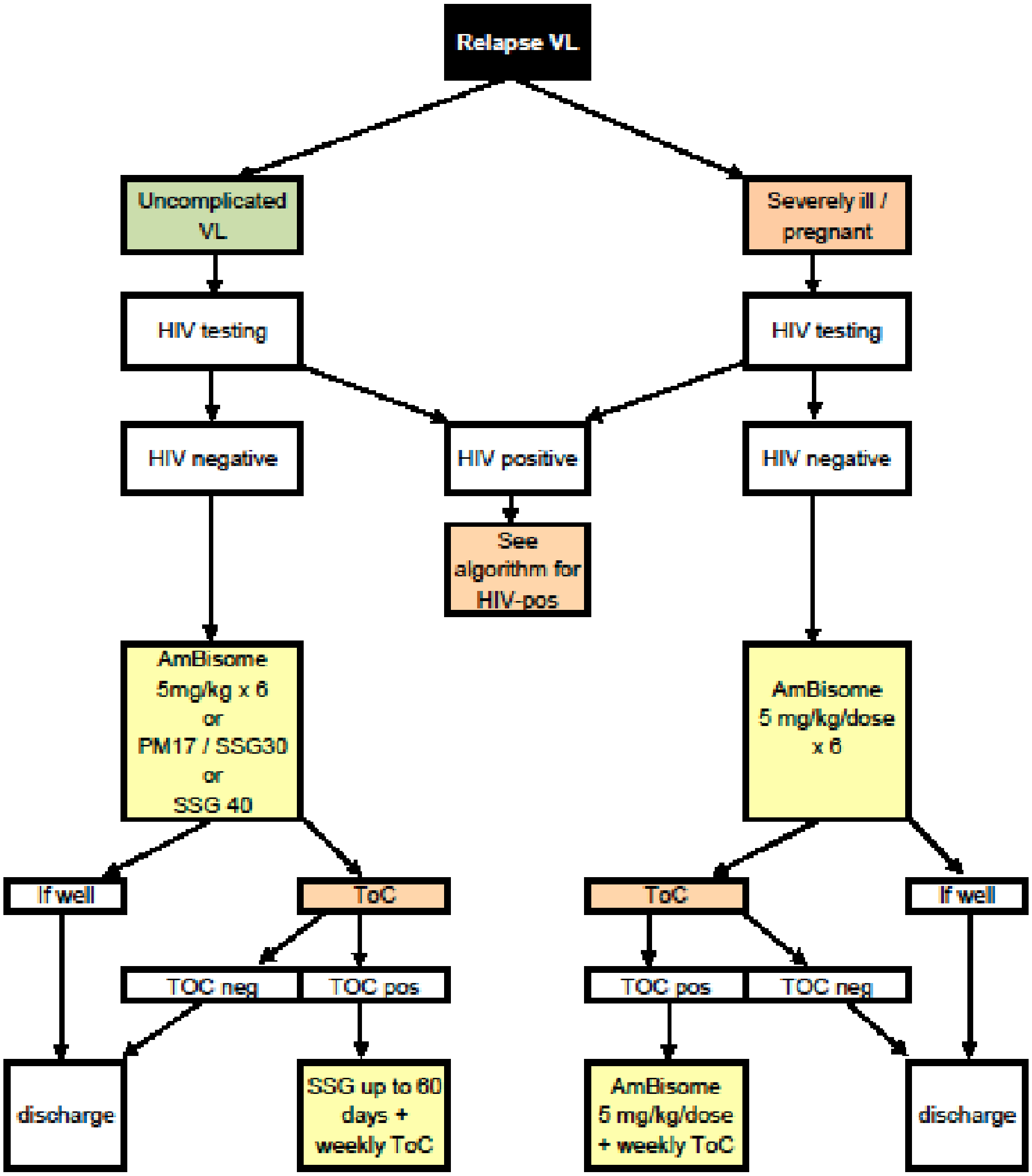
- A patient who is diagnosed with **VL for the first time is called** a **primary VL case**.
- **A definitive cure** is the **absence of VL signs and symptoms and a negative test of cure 6 months after initial cure**, i.e., 6 months after active diseases treatment.
- **Patient follow-up** is important to establish a definite cure with proper evaluation on appointment or when presented with fever, loss of weight, anemia and splenomegaly.
    - For definitive cure, one looks at the **clinical picture of the patient**; tissue aspirate may not be necessary at follow-up sessions unless a relapse is clinically suspected.
- If a person returns with clinical features and a positive parasitology consistent with visceral Leishmaniasis, after having been successfully treated for primary VL and discharged improved or with a negative test of cure (TOC), the patient is known as **relapse VL case.**

- It is impossible to differentiate relapse from new infection but various molecular studies proved relapse to be more common than re-infection.
- In **immune-competent** individuals**, VL relapses can occur in up to 5% of** the patients treated, whereas VL relapses can occur in **up to 50% in HIV/VL co-infected** cases.
- Most relapses occur within the first 6 months of initial treatment and are referred to as a first relapse if the relapse occurs for the first time and subsequent relapses are called second, third and so on depending on the number of relapses.
- **Risk factors for a VL relapse in HIV patients** are:
    - AIDS patients not on ART
    - Low CD4+ count
    - Previous VL episodes and failure to achieve clinical or parasitological cure during the first episode.
- ART could help to delay VL relapse but it does not prevent it. Sometimes relapses tend to have a higher parasite load and are often difficult to treat.

Treatment Regimens for First VL Relapse (see the Treatment Algorithm!)

- If possible, the regimen used for the treatment of relapses should be a different drug than that used for primary VL.
- The use of combination therapy with SSG and Paromomycin is recommended if it was not used for the treatment of prior VL episodes.
- When choosing a drug for treating a relapse the response to the initial treatment should be considered.
- The following regimens are recommended for the treatment of VL relapses
    - **Liposomal amphotericin B 5mg/kg/day** for a period of 6 days.
        - The treatment period can be extended up to 14 doses for better therapeutic advantages.
    - **SSG 20 mg/kg/day** for 40days until 2 consecutive weekly aspirates for parasitology
      are negative.
        - If Test of cure (TOC) is still positive, SSG should be given for a total of 60 days with close monitoring of drug toxicity and TOC checked again, if positivity persists, then 2nd line treatment must be used.
    - SSG/PM combination: SSG (30 days) and Paromomycin (17 days) can be used for VL relapse treatment.

Visceral Leishmaniasis treatment algorithm: Relapse VL


Relapse VL
Uncomplicated VL
Severely ill / pregnant
HIV testing
HIV testing
HIV negative
HIV positive
HIV negative
See algorithm for HIV-pos
AmBisome 5mg/kg x 6 or PM17 / SSG30 or SSG 40
AmBisome 5 mg/kg/dose x 6
If well
ToC
ToC
If well
TOC neg
TOC pos
TOC pos
TOC neg
discharge
SSG up to 60 days + weekly ToC
AmBisome 5 mg/kg/dose + weekly ToC
discharge

Note:

- Severely ill VL patients may require an extended dose of AmBisome if the test of cure (TOC) is positive after the end of 40mg/kg total dose of AmBisome.
- Patients with an extended dose of SSG require close safety monitoring.

13.2.4 Treatment of VL by Drug Interruption

- VL treatment can be interrupted by the treating clinician due to a medical reason by the treating clinician or by a failure of the patient.
- These patients are at high risk and also potential sources of disease transmission. Therefore, they should be treated.
- The treatment of VL after drug interruption depends on the duration of the interruption period as summarized in the table below:

The duration of treatment interruption	Action
< 5 days	**Continue the same treatment** until the full course **without compensating the missed treatment days.**
between 5 - 10 days	**Continue** the same treatment until the full course but **with compensation.**
> 10 days	**Restart treatment as day one.**

- These group of patients require test of cure (ToC) at the end of the treatment

Prognosis of VL Treatment

- **If untreated, VL is invariably fatal.** In a well-established treatment center, the **mortality** of patients **with VL treatment is below 10%.**
- Predictors of **bad prognosis** are;
  - AIDS patients with a low CD4 count
  - Very young or very old patients
  - Patients with suffer from the disease for more than 5 months prior to their presentation
  - Severe anemia
  - Severe malnutrition
  - Severe opportunistic infections
  - Thrombocytopenia
  - Relapsing course of the disease
  - Patients with vomiting
  - Patients in a state of collapse, and
  - Patients without secondary prophylaxis.

13.2.5 RVI - VL co infection

- **VL is an AIDS-defining condition** and co-infected patients present the WHO stage 4 (CDC stage C) of the disease.
- They have very low CD4+ cell counts and high viral loads (1000 to 1 million copies).
- In some parts of Ethiopia (e.g. Humera), about 30% of all VL patients are co-infected with HIV.
- The HIV/AIDS pandemic has modified the natural history of the Leishmaniasis disease.

- HIV infection increases the risk of developing VL by a factor between 100 and 1000 in endemic areas.
- It reduces the likelihood of therapeutic response, and greatly increases the probability of relapse.
- At the same time, VL promotes the clinical progression of the HIV disease and the development of AIDS-defining conditions.
- As the two diseases target similar immune cells, together they exert a synergistic damaging effect on the cellular immune response with a significant reduction of the TLC and CD4 cells.
- Atypical presentations of Leishmaniasis are reported in HIV patients, especially in those with a CD4 count less than 200-cells/μL.
- Relapses are more common in this group of patients.

Diagnosis

- Disease manifestations of VL in HIV-infected individuals without severe immuno-suppression are similar to those in immuno-competent persons.
- Among those **with advanced immuno-suppression** and low CD4+ T-lymphocyte counts, manifestations of Leishmaniasis may be **more severe, atypical and with a chronic and relapsing course after treatment**.
- Although a deficit in host humoral and cellular response induced by both, HIV and Leishmania infections, results in a somewhat reduced sensitivity of serological and delayed-type IV hypersensitivity-based tests, studies in Ethiopian co-infected patients have demonstrated acceptable sensitivity.
- **The gold standard for the diagnosis** of Leishmaniasis in HIV-infected patients remains the **isolation or identification of the parasite** in spleen, lymph node or bone marrow aspiration.
- Amastigotes can also be found in the peripheral blood of a proportion of HIV-infected individuals.
- Where HIV counseling and access to antiretroviral treatment are available, all VL patients should be screened for HIV. Vice versa, in endemic foci for VL, the HIV services should suspect VL in patients with clinical symptoms for VL or unexplained deterioration of an HIV patient after other opportunistic infections are ruled out.
- The presence of a HIV co-infection may alter the clinical presentation of patients so that atypical sites (non-reticuloendothelial organs) tend to be more involved. These include;
  - Oral mucosa
  - Gastrointestinal and
  - Concomitant diffuse skin involvement by the parasite
- Generally, the presence of a co-infection with HIV alters;
  - The clinical picture
  - The laboratory diagnosis and interpretation
  - The response to treatment
  - The occurrence of side effects, and
  - The frequency of recurrences after treatment.

Treatment of First Episode (Primary) *Kala Azar* in VL/HIV Co-Infected Patients

(see the Treatment Algorithm below)

- If VL is present in an HIV-positive patient, **ART should be started after VL treatment**, **regardless of the CD4+ cell count**.
- When there is a history of VL, but the patient is currently asymptomatic, a CD4+ count should be done and the national HIV treatment guidelines should be followed.
- **Start ART ASAP** to prevent further opportunistic infections and VL relapses, although **ART alone will not prevent VL relapses**.
- All anti-Leishmanial drugs are less effective in HIV-positive patients and the risk of relapse is high with them.
- Most relapses occur within 3-9 months, successive relapses become less typical and less acute, but more frequent.
- Moreover, with each relapse, patients become less responsive to treatment and eventually unresponsive to all drugs.
- Due to the overlapping toxicity between drugs (SSG and Amphotericin B) and some of the ARVs, ART should be initiated after completing VL treatment, unless the risk of delaying ART outweighs the risk of potential drug toxicity.
- In **patients already on ART**, VL treatment with **AmBisome is preferred** and **ART can be continued.**
- **SSG is more toxic in HIV patients**, necessitating careful monitoring.
- It is advisable to provide bed nets to VL/HIV co-infected patients because it might help in reducing the risk of transmission.
- **Anti-leishmanial drug combination therapy** may be the way to delay the emergence of resistance and increase antimicrobial activity. However, it is probable that even drug combinations will not prevent relapses altogether, leaving ART as the key in reducing and postponing relapses.

First-Line Drugs for First Episode (Primary) *Kala Azar* in VL/HIV Co-Infected Patients:

- **AmBisome (LAmB)**
  - AmBisome with a total dose of 40mg/kg in divided dose can be used for the treatment of VL in HIV co-infected individuals.
  - If TOC is **still positive** but with a significant parasite load reduction, the treatment with AmBisome can be **repeated until TOC becomes negative**.
  - If TOC positivity persists after repeating AmBisome, a compassionate treatment regimen should be used.
  - However**, if the parasite load does not decrease significantly** after the initial AmBisome 40mg/kg therapy, **SSG for 60 days** and above should be considered as therapy bearing in mind that safety monitoring by qualified medical personnel is necessary.
  - If even after the SSG therapy TOC is still positive, a compassionate regimen should be used.

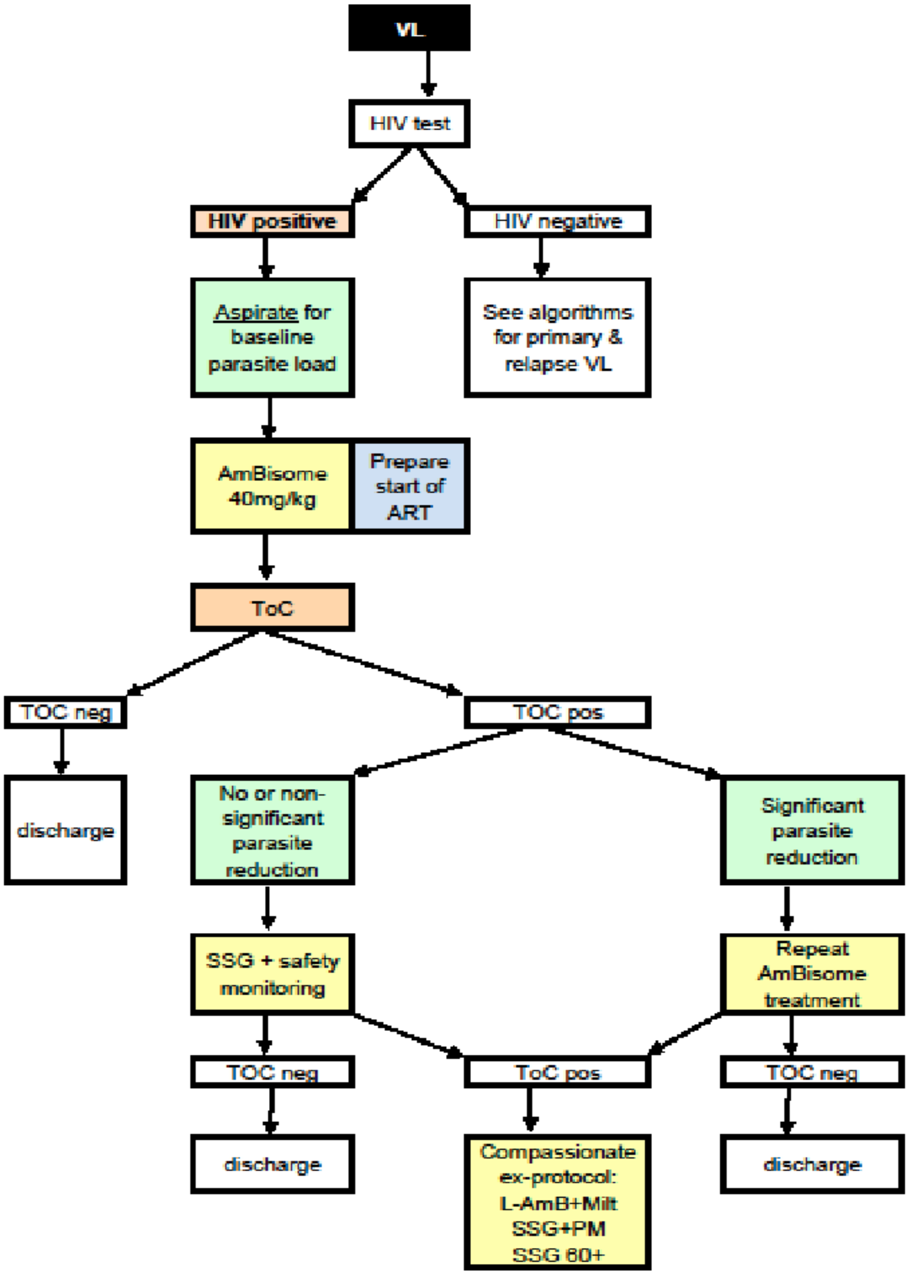
Second-Line Drug for Primary *Kala Azar* in VL/HIV Co-Infected Patients:

- **Pentavalent antimonials**
    - It is administered at a dose of **20mg antimony/kg/day, IV or IM, for 30 days**.
    - Adverse effects of the drug are more frequent in HIV infected patients.

Risk factors for death

- Risk factors for death That should be considered for all VL patients (with more emphasis for VL/HIV co-infected individuals) include;
    - Malnutrition
    - Concomitant opportunistic infection (TB or pneumonia)
    - Diarrhea or vomiting
    - Anemia
    - Bleeding and
    - Signs of toxicity during treatment (heart failure, arrhythmia, pancreatitis, jaundice, kidney failure, anemia, severe vomiting or diarrhea).
- After treatment of the first episode, assess for fever, weight, general condition, spleen size, and hematologic values to see the clinical improvement and ideally demonstrate parasitological cure (TOC) to endure that discharge is appropriate.
- If the test is positive, continue treatment, or substitute to a second-line regimen and exclude other opportunistic infections

Visceral Leishmaniasis treatment algorithm: HIV co-infected VL


VL
HIV test
HIV positive
HIV negative
Aspirate for baseline parasite load
See algorithms for primary & relapse VL
AmBisome 40mg/kg
Prepare start of ART
ToC
TOC neg
TOC pos
discharge
No or non-significant parasite reduction
Significant parasite reduction
SSG + safety monitoring
Repeat AmBisome treatment
TOC neg
ToC pos
TOC neg
discharge
Compassionate ex-protocol: L-AmB+Milt SSG+PM SSG 60+
discharge

Note:

In VL/HIV co-infected individuals, SSG 60+ may be considered while safety monitoring is warranted to the patient.

The 40mg/kg AmBisome schedule is on days 1 to 5 and then on the 10th, 17th and 24th day.

If the Test of cure (TOC) is positive after treatment with AmBisome 40mg total dose, compassionate treatment may be required. These include SSG/PM, SSG 60+, AmBisome /Miltefosine combinations, etc.

Management of VL Relapses in VL/HIV Co-Infected Patients

- Relapse of VL is a common phenomenon in HIV co-infected cases.
- This poses challenges to the control of Leishmaniasis.
- The drug chosen to treat relapse should be different from that used to treat the first episode. However, in case of multiple relapses, the drug of choice should not be a drug that has shown to be ineffective during any of the previous treatment episodes.
- To avoid the development of drug resistance as a consequence of repeated relapses, and to increase treatment efficacy, combinations of drugs should ideally be used. However, there is still a lack of evidence for the best combination for co-infected patients.
- The physician's decision on combination treatment or compassionate treatment should, therefore, be made on an individual basis.
- Due to lower efficacy of anti-Leishmanial drugs in HIV/VL extended treatment courses may be required to achieve cure.
- In order to distinguish between drug unresponsiveness and partial or slow drug responsiveness, it is recommended to do a TOC at the end of the standard treatment.
    - If there has been no parasitological response to treatment (demonstrated by the same parasite grade found in the TOC as for diagnosis, or, alternatively,) drug unresponsiveness is demonstrated, and treatment should be continued with another anti-Leishmanial drug
    - If standard treatment has resulted in a partial but significant parasitological response (demonstrated by parasite density in the TOC being at least two grades lower compared to the diagnostic assessment) treatment with the same drug may be continued until two subsequent negative TOCs have been obtained.

13.2.6 Post kala-azar Dermal Leishmaniasis (PKDL)

- **VL due to *L. donovani* occurs with a post treatment complication** called PKDL.
- PKDL is characterized by the occurrence of **painless skin lesions** relatively common towards the end of treatment (**more common in Sudan** with about 50% of the cases) or shortly *after treatment*.
- PKDL is **rare in Ethiopian VL patients** but it is **relatively common in *Leishmanial* HIV co-infection.**
- PKDL patients harbor Leishmania parasites in the skin lesions and these can be potential sources of infection and disease transmission.
- Patients should be advised to seek medical attention and use impregnated bed nets if they develop skin rash following treatment.
- Depending on the severity of the lesion, PKDL can be graded (see table below) which will facilitate treatment decisions.
- Occasionally, **PKDL may occur** prior to the VL **(Pre-*kala azar* dermal Leishmaniasis)** or concomitantly **(para-*kala azar* dermal Leishmaniasis)** to the active VL disease.

Table; Grading PKDL Lesions:	
Grade 1	**Scattered macular, papular or nodular skin rashes** mainly on the **face and around the mouth**, with or without some lesions on the upper chest and upper limbs.

Grade 2	**Dense** macular, papular or nodular rashes covering **most of the face and which are extending to the chest, back, upper arms and legs.** If lesions are extensive or blackened, this is called **PKDL grade 2 severe form.**
Grade 3	**Dense** macular, papular or nodular rashes **covering most of the body** including hands and feet. Here, **crusting, ulcers, sloughing, scaling, blackening of skin and spreading** of the lesions to mucosa of the lips and the palate occur.

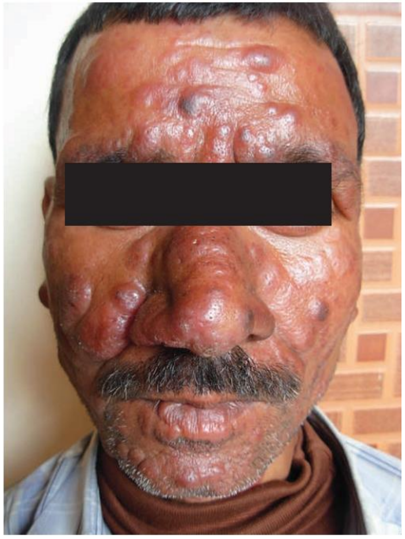

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FIGURE 221-4 *(Harrison 20th edition);* **Post - kala-azar dermal leishmaniasis in an Indian patient.** Note nodules of varying size involving the entire face. The face is erythematous, and the surface of some of the large nodules is discolored.

Treatment of PKDL (Pre-, Para-, Post-*Kala Azar* Dermal Leishmaniasis)

- Not all PKDL patients need treatment; decision can be made depending on severity of the lesion (PKDL Grade).
- As PKDL patients harbor the parasite, they can be a potential source of infection and disease transmission.
- Patients should be advised to seek medical attention and use impregnated bed nets (ITNs) if they develop skin rash following VL treatment.
- Most PKDL cases are Grade 1. The majority of the lesions heal spontaneously within 12 months but need close follow-up.
- **Indication for treatment;**
  - PKDL patients with a **severe** form of **Grade 2** and **Grade 3** lesions and/or disfiguring disease
  - Those with lesions that have existed for more than 6 months
  - Those with concomitant anterior uveitis/conjunctivitis and
  - Young children with oral lesions that interfere with feeding

Antileishmanial options

- **Antimonials (SSG 20mg/kg/day for 30 days).**

  - Treat until lesions are flattened or are no longer palpable but discoloration can still be visible.
  - Do not wait until lesions disappear, sometimes longer treatment courses are needed.
  - Follow-up is passive as there are no parasite criteria for cure due to the difficulties of demonstrating the parasite in the lesions.
  - SSG toxicity is rare in PKDL treatment.
- **Miltefosine,100mg daily for 28 days**
  - Miltefosine has shown a beneficial effect for the management of PKDL in large series of Indian patients.
  - It demonstrated a shorter duration of therapy and a better compliance by increasing the dose or duration of therapy.
  - Instead of 100mg daily for 12 weeks, increasing the daily dose by using 50mg twice or trice per day could shorten the duration of therapy.
  - In Ethiopia, two cases of PKDL have been successfully treated with Miltefosine 100mg daily for 28 days. Thus, Miltefosine may provide an opportunity for treating PKDL.

13.2.7 VL Treatment in Special Groups

Pregnancy:

- Evidence for the safety of anti-Leishmanial drugs is scarce.
- **No VL drug is proven to be safe** in pregnancy.
- Pregnant women should, therefore, be treated with the safest available anti-Leishmanial drug as the disease is life threatening for the mother and may have consequences for the fetus.
- **Liposomal Amphotericin B is relatively safe and effective**, while conventional amphotericin B is nephrotoxic. Pregnant women are particularly vulnerable to this.
- **Dosage and administration are similar to other group of patients**.
- In situations where there is no option, **risk-benefit has to be assessed in the use of SSG** especially in the first trimester.

Malaria and VL:

Due to the **overlap in epidemiologic occurrence of both diseases**, it is not uncommon to find these fatal diseases occurring simultaneously.

Malaria will be severe in patients with VL because VL patients are already weak, with an ineffective spleen function and are already anemic.

Screening for malaria is recommended for all VL patients admitted from malaria endemic areas.

Treatment of both diseases at a time needs attention due to the overlap of drug side effects.

The following points should be taken into considerations during the management of malaria-VL co-infection:

  - **SSG should not be used with quinine** (due to the cardio-toxicity of both drugs).
  - Use ACT (**Coartem) in uncomplicated falciparum malaria** cases or **Artemether (intramuscular) in severe malaria cases.**

  - If treatment with quinine is inevitable, **stop SSG while quinine is being given.** After quinine treatment is finished, **resume SSG to complete the recommended duration of treatment starting 24 hours after the last dose of quinine.**
  - If quinine needs to be used, **consider shortening quinine usage for 3-5 days and finish with Coartem full dose to help to resume SSG within a short period.**
  - **Consider Artemether as a suitable alternative for quinine.**

3. Management of Concomitant Infections in VL

- Patients with VL are generally immuno-compromized and can get infections with bacteria, parasites and mycobacteria
- **Pneumonia**
  - **It** is one of the commonest co-morbidities with VL leading to increased morbidity.
  - VL patients with pneumonia require vigorous treatment with **broad-spectrum antibiotics**.
  - **Consider also tuberculosis** if there is no response to an appropriate antibiotic treatment
- **Diarrhea**
  - **Diarrhea** is the principal cause of death in VL patients.
  - The diarrhea may be watery, mucoid or bloody with variable causative agents.
  - It needs aggressive therapy with **hydration and proper antibiotics.**
  - The choice of antibiotics is based on the result of **stool examination.**
- **Other infections** that can occur with VL, like **skin infections, cancrum oris, and otitis media**, also require treatment.

13.3. Cutaneous Leishmaniasis (CL) /ቁንጭር/

- ***L. aethiopica* causes more than 99.9% of the CL cases in Ethiopia**.
  - *L. major* and *L. tropica* have been isolated from sandfly vectors and one case of CL due to *L. tropica* was reported
- CL can be broadly divided into Old World and New World forms (see table from life cycle of leishmania above).
  - **Old World** CL caused by *Leishmania tropica* is anthroponotic and is confined to urban or suburban areas throughout its range.
    - Zoonotic CL is most commonly due to *Leishmania major*, which naturally parasitizes several species of desert rodents that act as reservoirs over wide areas of the Middle East, Africa, and central Asia.
  - **New World** CL is mainly zoonotic and is most often caused by *Leishmania mexicana, Leishmania (Viannia) panamensis*, and *Leishmania amazonensis*.
    - A wide range of forest animals act as reservoirs, and human infections with these species are predominantly rural.
- Local outbreaks of human disease are common.
- Major outbreaks currently affect Afghanistan, Syria, Iraq, Lebanon, and Turkey in association with refugees and population movement.

- CL is increasingly seen in tourists and military personnel on mission in CL-endemic regions of countries and as a co-infection in HIV-infected patients.
- ***Leishmania aethiopica*** **is restricted to the highlands of Ethiopia, Kenya, and Uganda**, where it is a natural parasite of hyraxes.

Clinical Features

- **A typical history (an insect bite followed by the events leading to ulceration) in a resident of or a traveler to an endemic focus strongly suggests CL.**
- A few days or weeks after the bite of a sandfly, **a papule develops and grows into a nodule that ulcerates over weeks or months.**
- The base of the ulcer, which is usually **painless, consists of necrotic tissue and crusted serum**, but **secondary bacterial infection** sometimes occurs.
- The **margins of the ulcer are raised and indurated.** Lesions may be **single or multiple** and vary in size from 0.5 to >3 cm **(see figure below)**.
- Lymphatic spread and lymph gland involvement may be **palpable LAP** and may precede the appearance of the skin lesion.
- There may be satellite lesions, especially in *L. major* and *L. tropica* infections
- The lesions **usually heal spontaneously after 2—15 months.** Lesions due to *L. major* and *L. mexicana* tend to heal rapidly, whereas those due to *L. tropica* and parasites of subspecies *Viannia* heal more slowly.
- *L. mexicana* is responsible for **chiclero's ulcer,** the so-called self-healing sore of Mexico.
- CL lesions on exposed body parts (e.g., the face and hands), **permanent scar formation, and social stigmatization may cause anxiety and depression** and may affect the quality of life of CL patients.

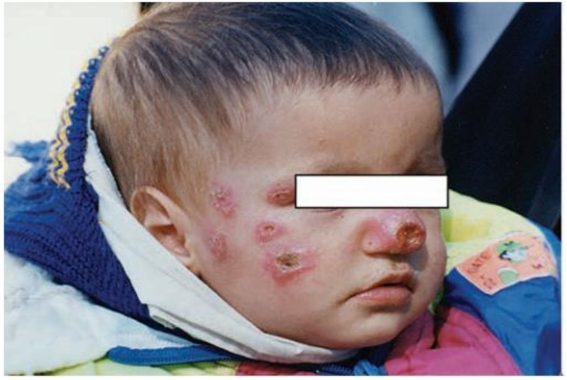


FIGURE 221-5 Cutaneous leishmaniasis in a Bolivian child. There are multiple ulcers resulting from several sandfly bites. The edges of the ulcers are raised.

Differential Diagnosis

- Cutaneous tuberculosis
- fungal infections
- leprosy
- sarcoidosis, and
- malignant ulcers

Laboratory Diagnosis

- **Demonstration of amastigotes in material obtained from a lesion remains the diagnostic gold standard.**
    - Microscopic examination of slit skin smears, aspirates, or biopsies of the lesion is used for detection of parasites.
- Culture of smear or biopsy material may yield *Leishmania*.
- PCR is more sensitive than microscopy and culture and allows identification of *Leishmania* to the species level.

Treatment of Cutaneous Leishmaniasis

- The **goals of therapy in cutaneous Leishmaniasis** are;
    - To kill the parasite
    - To control its spread into mucosal disease,
    - To accelerate healing and to reduce scarring, especially in cosmetic sites.
- Although lesions **heal spontaneously in the majority of cases**, their spread or persistence indicates that treatment may be needed.
- **Treatment Options** → There are 3 options for treatment of CL, which should be discussed with the patient:
    - To withhold treatment,
    - Topical or local treatment, and
    - Treatment with systemic drugs.
- The decision which option to offer depends on the nature of the lesions and the ability of the patient to attend for treatment and to return for follow-up.

Withhold Treatment

As the majority of CL lesions heal spontaneously within a year, the best treatment for patients **who fulfill the following criteria** are to withhold treatment or to accept local treatment:

- Fewer than 2 lesions requiring immediate treatment;
- Lesions are smaller than 5 cm in diameter
- Absence of indurations or firmness of surrounding skin, on palpation no mucosal involvement, or lesions are not close to the nose or the lips;
- Lesions are not on the border of the lip, the nostrils or the eyes;
- No potentially disfiguring or disabling lesion (on the nose, the joints, the toes, or the fingers);
- No immuno-suppression

- Patients who fulfill the above criteria need follow-ups to evaluate the progress of the lesion(s) and to decide on their subsequent treatment.

B. Local Treatments

- A bacterial superinfection is uncommon, but when suspected, it should be managed with appropriate antibiotics

- wound care before starting the CL treatment.
- **Two methods of local CL treatment are commonly used in Ethiopia**. These are;
  - Intra-lesional administration of Sodium Stibogluconate (SSG)
  - Cryotherapy
- Other local CL treatment methods, not applicable currently in Ethiopia, include;
  - Curettage Under Local Anesthetic
  - Thermotherapy under Local Anesthetic
  - Topical Ointments
    - One or a few small lesions due to "self-healing species" can be treated with topical agents
    - In Peru, Topical imiquimod (5 - 7.5%) plus parenteral antimonials have been shown to cure CL more rapidly than antimonials alone.
    - An **ointment containing 15% paromomycin** sulfate, either alone or with 0.5% gentamicin **or** 12% methylbenzonium chloride for 20 days.
- **Intra-Lesion Administration of SSG:**
  - Small lesions (≤3 cm in diameter) may conveniently be treated **weekly with intra-lesional SSG for 4 to 6 weeks (until cure)**
    - an intralesional injection of a pentavalent antimonial **at a dose adequate to blanch the lesion (0.2 - 2 mL).**
  - But training and meticulous technique are essential for this method, in which *the injection must be administered intralesionally* and *NOT beneath or around the lesion*.
  - Using a 1ml syringe with a fine intradermal needle, undiluted SSG is injected into the lesion until it blanches. **About 0.2-0.5ml** may be adequate **for the first injection** of a small nodule.
  - **Weekly reassessment** is recommended with SSG re-injections **if clinically indicated.**
  - **Once the lesion has been disrupted**, up to **2ml SSG may be needed to infiltrate residual thickened areas**.

C. Systemic Treatment

- Systemic treatment is indicated for;
  - Lesions over the face, hands, or joints
  - Multiple lesions; More than 4 lesions
  - Large ulcers
  - Lymphatic spread; Lesions accompanied by nodular lymphangitis
  - CL with the potential for development of ML
  - CL in HIV-co-infected patients.
  - ML or DCL
  - Lesions which are bothersome to the patient but unsuitable for local treatment
  - Large lesions unsuitable for local treatment
  - Patients not responding to topical treatment

first-line drug for all forms of CL

- **Pentavalent Antimony Compounds (SSG) or Meglumine Antimoniate (MA)**

- Dosage: **20mg SSG/kg/day IM or IV for 4 - 8 weeks**[16]
-

Plus

- **Paromomycin (16 mg/kg, IM daily for 20 to 30 days)**
  - **CL due to *L. aethiopica*, which responds to paromomycin but not to antimonials. So, in Ethiopia SSG is used with paromomycin** due to Its action as a synergistic with SSG against isolates of *L. aethiopica*
  - CL caused by *Leishmania (Viannia) guyanensis*, for which pentamidine isethionate is the drug of choice (two injections of 4 mg of salt/kg separated by a 48-h interval) but not SSG

- Relapses usually respond to a second course of treatment

Alternative

- **Miltefosine and Liposomal Amphotericin B**
  - Miltefosine (2.5 mg/kg for 28 days) and Liposomal Amphotericin B are effective in the treatment of CL in several countries, but have not yet been used for *L. aethiopica* infections.

Adjuvant therapy

- Azoles and triazoles have been used with mixed responses in both Old and New World CL, **but have not been adequately assessed for this indication** in clinical trials.
  - In *L. major* infection, **oral fluconazole (200 mg/d for 6 weeks**) resulted in a higher rate of cure and also cured infection faster.
  - **Ketoconazole (600 mg/d for 28 days**) is effective in CL due to *L. (V.) panamensis* and *L. mexicana* in Panama and Guatemala.

Follow-Up

- It is recommended that patients are routinely **followed up 6 weeks and 6 months after the completion of treatment.**
- Patients should be advised that recurrence is possible and that they should return if that happens. Most relapses occur within 6 months after treatment.

13.4 Diffuse Cutaneous Leishmaniasis (DCL

- DCL is a rare form of leishmaniasis caused by *L. amazonensis* and *L. mexicana* in South and Central America and **by *L. aethiopica* in Ethiopia and Kenya.**
- DCL is characterized by the lack of a cell-mediated immune response to the parasite, the uncontrolled multiplication of which thus continues unabated.
- Profound immunosuppression leads to widespread cutaneous disease.
- Lesions may **initially be confined to the face or a limb** but **spread over months or years** to other areas of the skin.

---

[16] Harrison [20th edition] recommends SSG, **20 mg/kg for 20 days,** national Guideline of leishmaniasis in Ethiopia [2nd edition] recommend for 4 to 8 weeks)

- They may be symmetrically or asymmetrically distributed and **include papules, nodules, plaques, and areas of diffuse infiltration**.
- These lesions **do not ulcerate**.
- The overlying skin is usually **erythematous in pale-skinned** patients.
- The lesions are teeming with parasites, which are therefore easy to recover.
- DCL **does not heal spontaneously and is difficult to treat**.
- If relapse and drug resistance are to be prevented, treatment should be continued for some time after lesions have healed and parasites can no longer be isolated.
- In the New World, **repeated 20-day courses of pentavalent antimonials** are given, **with an intervening drug-free period of 10 days**.
- Miltefosine has been used for several months with a good initial response. Combinations should be tried.
- **In Ethiopia, a combination of paromomycin (14 to 15 mg/kg per day) and sodium stibogluconate (10 mg/kg per day) is effective.**
    - paromomycin plus SSG in a synergistic dose, until amastigotes are no longer found in slit skin smears and then for several more weeks or months.

13.5 Mucocutaneous/Mucosal Leishmaniasis (ML)

- ML is typically caused by *L. (V.) braziliensis* and rarely by *L. amazonensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis*.
    - In *L. (V.) braziliensis* infections, cutaneous lesions may be simultaneously accompanied by mucosal spread of the disease or followed by spread years later.
- Young men with chronic lesions of CL are at particular risk.
- Overall, ~3% of infected persons develop ML.
- Not every patient with ML has a history of prior CL.
- ML is almost entirely confined to the Americas. In rare cases, ML may also be caused by Old World species like ***L. major,*** *L. infantum* (*L. chagasi*), or ***L. donovani***.

Clinical Features

- The parasite spreads via the lymphatics or the bloodstream to **mucosal tissues of the upper respiratory tract**.
- Intense inflammation leads to **destruction, and severe disability ensues**.
- **Lesions in or around the nose or mouth (**see figure below**) are the typical presentation of ML.**
- Patients usually provide **a history of self-healed CL preceding ML by 1 to 5 years.**
- **Typically,** ML presents as **nasal stuffiness and bleeding followed by destruction of nasal cartilage,perforation of the nasal septum, and collapse of the nasal bridge**.
- Subsequent involvement of the pharynx and larynx leads to **difficulty in swallowing and phonation.**
- The lips, cheeks, and soft palate may also be affected.
- **Secondary bacterial infection is common**, and **aspiration pneumonia** may be fatal.

- **ML does not heal spontaneously.**

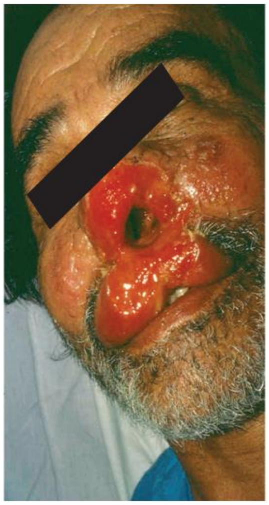


FIGURE 221-6; **Mucosal leishmaniasis in a Brazilian patient**. There is extensive inflammation around the nose and mouth, destruction of the nasal mucosa, ulceration of the upper lip and nose, and destruction of the nasal septum.

Laboratory Diagnosis

- **Tissue biopsy** is essential for identification of parasites, but the rate of detection is poor unless PCR techniques are used.

Treatment of Mucosal Leishmaniasis

- The regimen of choice is a pentavalent antimonial agent administered at a dose of **20 mg of SSG/kg for 30 days**.
- Patients with ML require long-term follow-up with repeated oropharyngeal and nasal examination.
- With **failure of therapy** or relapse, patients may receive another course of an antimonial but then become unresponsive, presumably because of resistance in the parasite.
    - In this situation, AmB should be used. An AmB deoxycholate dose totaling **25 - 45 mg/kg** is appropriate.
    - **LAmB, 2 - 3 mg/kg for 20** days is considered adequate.
- Miltefosine (2.5 mg/kg for 28 days).
- The more extensive the disease, the worse the prognosis; thus prompt, effective treatment and regular follow-up are essential.

Prevention and Control

- Vector Control
    - Insecticide Application
    - Use of Long-Lasting Insecticide Treated Nets (LLITN)

  - Repellents (Chemical or Natural)
  - Combination of several control methods
- Health Education and Social Mobilization through health development army
- Information System → Integrated Disease Surveillance (IDS) is the major strategy and mainstay of the Disease Surveillance in Ethiopia.

Chapter 14; Hematologic Malignancy (የደም ካንሰር)

Dr. Asmare.W

14.1 Leukemia

- Leukemia is a clonal, neoplastic disorder characterized by proliferation and accumulation of immature and malignantly transformed cells in the bone marrow and peripheral blood.
- Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its *acute* and *chronic* forms:
  - **Acute leukemia** is characterized by a rapid increase in the number of **immature** blood cells. The crowding that results from such cells makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia because of the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children.
  - **Chronic leukemia** is characterized by the excessive buildup of relatively **mature**, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal, resulting in many abnormal white blood cells. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukemia mostly occurs in older people, but can occur in any age group.
- Additionally, the diseases are subdivided according to which kind of blood cell is affected. This divides leukemia into lymphoblastic or *lymphocytic leukemia* and myeloid or *myelogenous leukemia*
  - acute myelogenous leukemia (AML)
  - chronic myelogenous leukemia (CML)
  - acute lymphoblastic leukemia (ALL)
  - chronic lymphocytic leukemia (CLL)

1) Acute myelogenous leukemia (AML)

- It is a neoplastic disease characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal undifferentiated cells of the hematopoietic system.
- This leukemia comprises a spectrum of malignancies that, untreated, range from rapidly fatal to slowly growing.
- AML incidence increases with age; it is 1.7 in individuals age <65 years and 15.9 in those age >65 years. The median age at diagnosis is 67 years

EPIDEMIOLOGY

- AML is the most common acute leukemia in adults and accounts for approximately 80 % of cases in this group. In contrast, AML accounts for < 10 % of acute leukemias in children < 10 years of age.
- In the United States and Europe, the incidence is reported as 3 to 5 cases per 100,000 population.
- In adults, the median age at diagnosis is approximately 65 years.
- The incidence increases with age with approximately 2 and 20 cases per 100,000 population for those under or over 65 years, respectively.
- The male : female ratio is approximately 5:3.
- This incidence is similar among persons of different races.

ETIOLOGY;

- Those have been implicated in the development of AML include.
  - Heredity
  - Radiation
  - Chemical and other occupational exposures
  - Drugs
- No direct evidence suggests a viral etiology.

CLASSIFICATION

- Following diagnosis, AML is classified using the WHO classification system based upon a combination of morphology, immunophenotype, genetics, and clinical features.
- The classification attempts to identify biologic entities in the hopes that future work will elucidate molecular pathways that might be amenable to targeted therapies.
- **There are six main groups of AML** recognized in this classification system
  - AML with recurrent genetic abnormalities
  - AML with myelodysplasia-related features
  - Therapy-related AML and MDS
  - AML, not otherwise specified
  - Myeloid sarcoma
  - Myeloid proliferations related to Down syndrome
- **The French-American-British (FAB) classification system divides AML into eight subtypes, M0 through to M7**, based on the type of cell from which the leukemia developed and its degree of maturity.

- AML with minimal differentiation (M0) — 6 % of AML, NOS (<5 % of total AML)
- AML without maturation (M1) — 25 % of AML, NOS (5 to 10 % of total AML)
- AML with maturation (M2) — 28 % of AML, NOS (10 to 14 % of total AML)
- Acute myelomonocytic leukemia (M4) — 21 % of AML, NOS (5 to 10 % of total AML)
- Acute monoblastic and monocytic leukemia (M5) — 15 % of AML, NOS (5 to 10 % of total AML)
- Pure erythroid leukemia (M6) — 4 % of AML, NOS (<5 % of total AML)
- Acute megakaryoblastic leukemia (M7) — 1 % of AML, NOS (<1 % of total AML

CLINICAL PRESENTATION

- Symptoms Patients with AML most often present with nonspecific symptoms that begin gradually or abruptly and are the consequence of anemia, leukocytosis, leukopenia or leukocyte dysfunction, or thrombocytopenia. Nearly half have had symptoms for ≤3 months before the leukemia was diagnosed.
- Half of patients mention fatigue as the first symptom, but most complain of fatigue or weakness at the time of diagnosis. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in approximately 10% of patients. Signs of abnormal hemostasis (bleeding, easy bruising) are noted first in 5% of patients. On occasion, bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis is the presenting symptom
- Rarely patients may present with symptoms from a myeloid sarcoma that is a tumor mass consisting of myeloid blasts occurring at anatomic sites other than bone marrow. Sites involved are most commonly the skin, lymph node, gastrointestinal tract, soft tissue, and testis. This rare presentation, often characterized by chromosome aberrations [e.g., monosomy 7, trisomy 8, MLL rearrangement, inv(16), trisomy 4, t(8;21)], may precede or coincide with AML.
- General fatigue is present in the majority of patients and often precedes the diagnosis for a number of months.
- Pallor and weakness are common and attributed to the anemia.
- Bone pain is infrequent in adults with AML, although some individuals describe sternal discomfort or tenderness, occasionally with aching in the long bones. This may be especially severe in the lower extremities, due to expansion of the medullary cavity by the leukemic process.

Diagnosis

PATHOLOGIC FEATURES;

- **Peripheral blood**
  - Analysis of the peripheral blood at presentation usually reveals a normocytic, normochromic anemia that can vary in severity.
  - The reticulocyte count is normal or decreased.
  - Approximately 75 % of patients have platelet counts below 100,000 cells/microL (100 x 10^9/L) at diagnosis, and approximately 25 % will have counts below 25,000 cells/microL.
  - Both morphologic and functional platelet abnormalities may be seen.
  - The median leukocyte count at diagnosis is approximately 15,000 cells/microL; 20 % of patients have a leukocyte count above 100,000 cells/microL and 25 to 40 % of patients have a leukocyte count less than 5000 cells/microL.
  - The vast majority of patients (95 %) will have circulating myeloblasts that can be detected on the peripheral smear.
  - There may or may not be evidence of myelodysplasia.
- **Myeloblasts**
  - **They** are immature cells with large nuclei, usually with prominent nucleoli, and a variable amount of pale blue cytoplasm (sometimes with faint granulation) after staining with Wright Giemsa.
  - The nuclear to cytoplasmic ratio and morphology vary depending upon the maturity of the cell.
  - **Auer rods,** which are pathognomonic of myeloblasts, vary in frequency depending upon the AML subtype.
  - They can be identified as pink/red rod-like granular structures in the cytoplasm.
  - Sometimes the Auer rods are multiple, and sometimes they form a dense clump and are referred to as "Auer bodies."
- **A myeloperoxidase reaction**
  - It is easy to perform, can be done in less than a few minutes, and is a simple means of determining if the blasts are myeloid.
  - Absence of a reaction product does not rule out AML, as some cases are negative.
  - Evaluation of myeloperoxidase reactivity must be focused on the blast population and not on mature or maturing myeloid elements on the smear.
- **Flow cytometry**
  - Flow cytometry of the peripheral blood or marrow aspirate can identify circulating myeloblasts in the majority of patients by characteristic patterns of surface antigen expression.
  - The specific pattern differs among the AML subtypes, but the majority of cases express **CD34, HLA-DR, CD117, CD13, and CD33**.

- Myeloblasts may express T or B cell antigens, most commonly in cytogenetically defined subtypes of AML (eg, CD19 expression in AML with *RUNX1-RUNX1T1*, CD2 expression in APL) and in acute leukemias of ambiguous lineage (mixed phenotype acute leukemia [MPAL]).
- Care must be taken in interpreting the antigen profile, and in distinguishing AML from ALL or MPAL.
- In general, the panel of antigens analyzed must contain multiple myeloid, B and T cell markers; the presence of a single B or T cell marker (eg, CD19 or CD7) is insufficient for diagnosing MPAL.

Bone marrow biopsy and aspirate

Blast count

- Bone marrow aspiration and biopsy (usually unilateral) is a key component to the diagnosis of AML.
- The bone marrow is usually hypercellular due to a partial or almost total replacement of the normal cellular components of the marrow by immature or undifferentiated cells, although AML can sometimes present with a hypocellular marrow
- The bone marrow biopsy gives a general overview of the degree of involvement and specific histologic features associated with the process (eg, fibrosis, necrosis).
- The aspirate provides material for a 500-cell differential count to determine the percentage of blasts in the marrow; it also provides for detailed cytologic evaluation of the blasts and other cells that may be residual normal hematopoietic elements or abnormal cells maturing from the blasts.
- The differential count from the aspirate is critical because the blast percentage from the flow specimen may be influenced by hemodilution and artifacts produced by the variability by which the specimen is prepared (eg, red cell lysis techniques, density gradient centrifugation) and the approach through which different cell populations are selected for gating.

Cell origin

- The blasts in AML must be identified as cells of the myeloid, monocytic, erythroid, or megakaryocytic lineage and are distinguished from blasts of the lymphoid lineage seen in acute lymphoblastic leukemia. The non-lymphoid lineage of the AML blasts can be identified by any of the following:
  - The presence of an Auer rod on microscopy.
  - Cytochemical studies demonstrating positivity for Sudan black B, myeloperoxidase, chloroacetate esterase, or nonspecific esterase.
  - Flow cytometry identifying the expression of myeloid antigens. It is notable that up to 20 % of acute myeloid leukemias will

demonstrate co-expression of lymphoid markers (eg, CD7, CD19, CD2). The outcome after treatment with AML directed therapy is not affected by the co-expression of "lymphoid" antigens. "True" mixed phenotype acute leukemia (MPAL) is very uncommon and the diagnosis requires co-expression of unambiguous myeloid markers and the presence of lymphoid markers for B lineage.

- Specific cytogenetic abnormalities that are seen only in myeloid leukemias (eg, t(1;22)(p13;q13).

- **Cytogenetic features**
  - All patients with suspected AML should undergo metaphase cytogenetic analysis of their bone marrow biopsy specimen. Approximately 50 percent of patients with newly diagnosed AML will demonstrate cytogenetic abnormalities.
  - A combination of conventional karyotypic analysis plus reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescent in situ hybridization (FISH) for specific abnormalities can aid in the diagnosis, treatment, and post-treatment monitoring of patients with AML:

Molecular studies

- Abnormalities in certain genes, such as mutations in *FLT3*, nucleophosmin (*NPM1*), *KIT, CEBPA*, or *RUNX1* as well as gene expression profiles confer prognostic significance in adult patients with AML.
- *The diagnosis of AML requires both of the following:*
  - Documentation of bone marrow infiltration — Blast forms must account for at **least 20 %** of the total cells of the bone marrow aspirate (from a 500-cell differential count). Whether or not a blast percentage can be determined in the bone marrow, the presence of 20 percent or more blasts in the peripheral blood is also diagnostic of AML. Exceptions to this include leukemias with certain genetic abnormalities, such as those with t(8;21), inv(16), or t(15;17), and myeloid sarcoma, which are considered diagnostic of AML without regard to the blast count.
  - The leukemic cells must be of **myeloid origin** as demonstrated by either the presence of Auer rods, cytochemical positivity for myeloperoxidase, or presence of sufficient myeloid/monocytic markers recognized by immunophenotyping.

M3 morphology (acute promyelocytic leukemia)

- **Acute promyelocytic leukemia** (**APML**, **APL**) is the M3 subtype of acute myelogenous leukemia (AML), a cancer of the white blood cells.
- In APL, there is an abnormal accumulation of immature granulocytes called **promyelocytes.**

- The disease is characterized by a chromosomal translocation involving the retinoic acid receptor alpha (*RARα* or *RARA*) gene and is distinguished from other forms of AML by its responsiveness to all-*trans* retinoic acid (ATRA; also known as tretinoin) therapy
- APL is characterized by the presence of atypical promyelocytes in the peripheral blood and bone marrow. These cells are typically large with a creased, folded, or bilobed nucleus and cytoplasm filled with bright pink, reddish-blue or dark purple granules.
- APL represents a medical emergency with a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy. It is critical to start treatment with a differentiation agent (eg, all-trans retinoic acid) without delay as soon as the diagnosis is suspected based upon cytologic criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made.
- Depending on geographic variations, APL accounts for 5 to 20 percent of cases of AML.
- Patients with AML in general, and APL in particular, typically present with symptoms related to complications of pancytopenia (ie, anemia, neutropenia, and thrombocytopenia), including weakness and easy fatigability, infections of variable severity, and/or hemorrhagic findings such as gingival bleeding, ecchymoses, epistaxis, or menorrhagia. Combinations of these symptoms are common. Unique to APL is a presentation with **bleeding** secondary to **disseminated intravascular coagulation**.
- Coagulopathy associated with APL is complex and involves both disseminated intravascular coagulation (DIC) and primary hyper fibrinolysis and is either present at diagnosis or occurs soon after the initiation of cytotoxic chemotherapy. This complication constitutes a medical emergency, because, if left untreated, it can cause pulmonary or cerebrovascular hemorrhage in up to 40 percent of patients and a 10 to 20 percent incidence of early hemorrhagic death.
- adverse risk factors were a total white blood cell (WBC) count greater than 10,000/microL and a platelet count less than or equal to 40,000/microL. Using these two parameters, three prognostic categories could be distinguished, with the following estimated probabilities of three-year relapse-free survival (RFS):
    - **Low risk** — WBC ≤10,000/microL and platelets >40,000/microL; RFS 98 percent
    - **Intermediate** — WBC ≤10,000/microL and platelets ≤40,000/microL; RFS 89 percent
    - **High risk** — WBC >10,000/microL; RFS 70 percent
- APL is unique among leukemias due to its sensitivity to all-*trans* retinoic acid (ATRA; tretinoin), the acid form of vitamin A Unlike other chemotherapies, ATRA does not directly kill the malignant cells. ATRA induces the terminal differentiation of the leukemic promyelocytes, after which these differentiated

malignant cells undergo spontaneous apoptosis on their own. ATRA alone is capable of inducing remission but it is short-lived in the absence of concurrent "traditional" chemotherapy.

2) Chronic myelogenous leukemia (CML)

- CML, (a.k.a chronic myelocytic, chronic myelogenous, or chronic granulocytic leukemia) is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation.
- In addition to CML the other diseases classified as myeloproliferative are **polycythemia vera (PV)**, **essential thrombocythemia (ET)**, and **primary myelofibrosis**.
- CML is associated with the fusion of two genes: **BCR** (on chromosome 22) and **ABL1** (on chromosome 9) resulting in the **BCR-ABL1** fusion gene. This abnormal fusion typically results from a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11), that gives rise to an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. It is this derivative chromosome 22 which harbors the BCR-ABL1 fusion gene.
- The clinical hallmark of CML is the uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils. In the absence of treatment, CML has a triphasic or biphasic clinical course as it progresses from a chronic phase to an accelerated phase and on to a terminal blast crisis. Sometimes it goes from chronic phase directly to blast crisis, particularly when the blast phase is lymphoid.

EPIDEMIOLOGY

- CML accounts for approximately 15 to 20 percent of leukemias in adults. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance.
- The median age at presentation is approximately 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 10 years older. Exposure to ionizing radiation is the only known risk factor.

CLINICAL MANIFESTATIONS

- CML has a triphasic or biphasic clinical course:
  - **A chronic phase**, which is present at the time of diagnosis in approximately 85 percent of patients;
  - **An accelerated phase**, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment; defined as the presence of one of the following
    - Blast cells constituting 10 to 19% of the cells in the peripheral blood or bone marrow
    - Basophilia > 20% of the cells in the peripheral blood
    - Persistent thrombocytopenia <100,000/µl
    - Persistent thrombocytosis >100,000/µl unresponsive to therapy
    - Increasing spleen size and WBC count unresponsive to therapy
    - Cytogenic clonal evolution

  - **Blast crisis,** a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner. Defined as the presence of one of the following
    - Blasts ≥ 20% in the peripheral blood or bone marrow
    - Extramedullary blast proliferation, apart from the spleen
    - Large foci or clusters of blasts in the bone marrow biopsy
- The clinical findings at diagnosis of CML vary among reported series and also depend upon the stage of disease at diagnosis.
- **20 to 50 %** of patients are **asymptomatic**, with the disease first being suspected from routine blood tests.
- Among symptomatic patients, systemic symptoms are common such as
  - **fatigue** (34 percent**)**
  - **malaise** (3 percent)
  - weight loss (20 percent**)**
  - **excessive sweating** (15 percent)
  - **abdominal fullness** (15 percent), and
  - **bleeding episodes** due to platelet dysfunction (21 percent).
- Abdominal pain and discomfort may include **left upper quadrant pain** (sometimes referred to the left shoulder) and early satiety, due to the enlarged spleen with or without perisplenitis and/or splenic infarction.
- **Tenderness over the lower sternum**, due to an expanding bone marrow, is sometimes seen.
- **Acute gouty arthritis** may also present at this time, due to overproduction of uric acid.
- Other frequent findings include
  - **splenomegaly** (present in 48 and 76 percent in two series)
  - **anemia** (45 and 62 percent)
  - **WBC count above** 100,000/microL (52 and 72 percent), and
  - **platelet count** above 600,000 to 700,000/microL (15 and 34 percent).
- Involvement of extramedullary tissues such as the lymph nodes, skin, and soft tissues is generally limited to patients with blast crisis.
- In accelerated phase patients tend to be more symptomatic. Spleen size increases, and symptoms of anemia. The presentation in blast crisis phase like that of acute leukemia (infection, bleeding, and rapid deterioration in clinical status).

DIAGNOSIS

- **Peripheral blood**
  - The peripheral smear typically demonstrates a leukocytosis with a median white count of approximately 100,000/microL (range 12 to 1000/microL).
  - The white blood cell differential typically shows virtually all cells of the neutrophilic series, from myeloblasts to mature neutrophils with peaks in the percent myelocytes and segmented neutrophils.
  - Blasts typically account for less than 2 percent.
  - The presence of a greater percent of myelocytes than the more mature metamyelocytes ("leukemic hiatus" or "myelocyte bulge") is one of the classic findings in CML.

- The platelet count can be normal or elevated. Platelet counts above 600,000/microL are seen in 15 to 30 percent of patients. Low platelet counts or thrombocytopenia, if present at diagnosis, should make one reconsider other diagnostic possibilities, such as one of the myelodysplastic syndromes.
- A normochromic, normocytic anemia is seen in 45 to 60 percent of patients.

- Bone marrow biopsy
  - Bone marrow aspiration and biopsy demonstrates granulocytic hyperplasia with a maturation pattern that reflects that seen in the peripheral smear.
  - There is usually a widened area of immature neutrophils in the paratrabecular cuff and mature neutrophils are found in the intertrabecular areas.
  - The peripheral blood and bone marrow aspirate differential count are key components of determining the disease stage.
  - In general, peripheral blood and bone marrow blasts between 10 and 19 percent are diagnostic of accelerated phase disease, while blasts over 20 percent are diagnostic of blast crisis.
- Genetics
  - Genetic testing for the Philadelphia chromosome, the BCR-ABL1 fusion gene or the fusion mRNA gene product is done by conventional cytogenetic analysis (karyotyping), fluorescence in situ hybridization (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR).
  - Southern blot techniques to identify BCR-ABL1 gene rearrangements were used in the past, but are time consuming and no longer employed as a routine diagnostic test. Evaluating for BCR-ABL1 protein by Western blot analysis is also not typically done. All patients with CML have evidence of the Philadelphia chromosome (Ph), the BCR-ABL1 fusion gene or its product, the BCR-ABL1 fusion mRNA by at least one of these tests.

The diagnosis of CML is first suspected by identifying the typical findings in the blood and bone marrow, and then confirmed by the demonstration of the Philadelphia chromosome, the BCR-ABL1 fusion gene or the BCR-ABL1 fusion mRNA by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR).

TREATMENT

- **Overview** – the two main treatment options for patients with newly diagnosed chronic phase (CP) CML are:
  - BCR-ABL1 tyrosine kinase inhibitors (TKIs), such as **imatinib**, dasatinib, nilotinib, bosutinib, and radotinib.
  - Allogeneic hematopoietic cell transplantation (HCT).

Acute lymphoblastic leukemia (ALL)

- **ALL**, is an acute form of leukemia characterized by the overproduction and accumulation of cancerous, immature white blood cells, known as lymphoblasts. In persons with ALL, lymphoblasts are overproduced in the bone marrow and continuously multiply, causing damage and death by inhibiting the production of normal cells (such as red and white blood cells and platelets) in the bone marrow and by spreading (infiltrating) to other organs.
- ALL is most common in childhood, with a peak incidence at 2—5 years of age and another peak in old age.
- ALL was one of the first cancers for which an effective chemotherapeutic treatment was developed.
- Antifolates like aminopterin and methotrexate were developed in the late 1940s by Sidney Farber and Yellapragada Subbarow.
- ALL is associated with exposure to radiation and chemicals in animals and humans.
- High level radiation exposure is a known risk factor for developing leukemia, as found by studies of survivors of atom bomb exposure in Hiroshima and Nagasaki.
- In animals, exposure to benzene and other chemicals can cause leukemia

EARLY SIGNS AND SYMPTOMS

- the most common presenting symptoms of ALL are nonspecific and may be difficult to distinguish from common, self-limited diseases of childhood. In a meta-analysis, more than half of children with childhood leukemia had at least one of the following five features on presentation: **palpable liver**, **palpable spleen**, **pallor**, **fever**, or **bruising**.
- **Hepatosplenomegaly** – Hepatomegaly (64 percent) and/or splenomegaly (61 percent) are the most common clinical findings in association with childhood leukemia. These abnormalities may also manifest as symptoms of anorexia, weight loss, abdominal distension or abdominal pain, or an abdominal mass noted by a family member or clinician.
- **Lymphadenopathy** – nearly half of children with ALL present with lymphadenopathy, which is one of the indications of extramedullary leukemic spread. As a general rule, a lymph node is considered enlarged **if it is >10 mm** in its greatest diameter. Exceptions to this rule include the following:
  - **Epitrochlear nodes** are enlarged if they are >5 mm.
  - **Inguinal nodes** are enlarged if they are >15 mm in greatest diameter.
  - **Cervical nodes** are enlarged if they are >20 mm.
- Lymphadenopathy associated with malignancy usually is **non tender**, **firm, rubbery, and matted**. Persistent or progressive lymphadenopathy that does not respond to antibiotic therapy suggests the need for more extensive evaluation.
- **Musculoskeletal pain** – although bone pain occurs commonly among children, particularly adolescents, it may be a symptom of ALL. Early bone marrow examination should be considered in any child who has persistent bone pain and peripheral blood abnormalities.

DIAGNOSTIC EVALUATION

- **Peripheral blood abnormalities**
  - most children with ALL have anemia and/or thrombocytopenia with either normal or slightly increased WBC counts, and lymphoblasts on peripheral smear.
  - These findings suggest the need for bone marrow examination, which should be performed for the following indications:
    - Atypical cells in the peripheral blood
    - Unexplained depression of more than one peripheral blood element (cytopenias). Cytopenias are defined as an absolute neutrophil count (ANC) of <500/microL, Hgb <8 g/dL, or a platelet count <150,000/microL.
    - Unexplained lymphadenopathy or hepatosplenomegaly associated with cytopenias
- **Morphology-**In the World Health Organization classification system for hematologic malignancies, the lymphoblastic neoplasms (which may present as leukemia and/or lymphoma) are divided into two general categories based upon lineage
  - Precursor B cell lymphoblastic leukemia/lymphoma, also called precursor B cell acute lymphoblastic leukemia (precursor B cell ALL)
  - Precursor T cell lymphoblastic leukemia/lymphoma (precursor T-LBL), also called precursor T cell acute lymphoblastic leukemia (T cell ALL)
  - These two entities are morphologically indistinguishable. On peripheral blood smears and bone marrow aspirates, lymphoblasts vary from small cells with scant cytoplasm, condensed nuclear chromatin, and indistinct nucleoli to larger cells with moderate amounts of cytoplasm, dispersed chromatin, and multiple nucleoli.
  - The former FAB L3 category is currently described as Burkitt lymphoma/leukemia in the WHO classification.

- **Immunophenotype**
  - leukemia cells in ALL are classified according to immunophenotype using an extensive panel of monoclonal antibodies to cell surface "cluster of differentiation" (CD) markers. Markers used to classify cells by lineage are the same as those used in adult ALL.
  - Approximately 70 to 80 percent of cases of childhood ALL are of B-precursor lineage (ie, precursor B cell leukemia or early pre-B cell ALL). B-precursor leukemia typically is **CD10+, CD19+, and sometimes CD20+.**
  - Leukemic lymphoblasts with the L3 morphology usually have markers for mature B cell ALL (**CDs 10 ± 19, 20, 22, 25, and surface immunoglobulin).**

  - Cases of T cell ALL (i.e, precursor T lymphoblastic leukemia), which comprise 15 to 17 percent of all cases of ALL, are positive for CD2, 3, 4, 5, 7, and 8.

- **Cytogenetics**
  - chromosomal abnormalities are common in childhood ALL.
  - Although not specifically used for diagnosis, cytogenetic findings are an essential part of the risk group stratification of childhood ALL and help to guide therapy.
  - Cytogenetics must be considered in the context of other risk factors and response to the first month of chemotherapy.
  - The diagnosis of central nervous system (CNS) leukemia requires one of the following:
    - Cytologic confirmation of the presence of leukemic cells in the cerebrospinal fluid (CSF)
    - Clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome
    - A tumor mass involving the CNS as determined by imaging studies
  - ALL can present clinically as either a mass lesion or as leukemia. Although the distinction in some patients is arbitrary, ALL is the preferred term in the US when the bone marrow contains **more than 25 percent lymphoblasts**, whereas lymphoma is the preferred term when the process is confined to a mass lesion with minimal or no blood and bone marrow involvement.
  - CNS involvement is often categorized into three groups:
    - CNS1 — no blasts in the CSF
    - CNS2 — <5 blasts in the CSF with or without RBC
    - CNS3 — >5 blasts in CSF

TREATMENT

- Chemotherapy is the initial treatment of choice. Most ALL patients will receive a combination of medications. There are no surgical options because of the body-wide distribution of the malignant cells.
- In general, cytotoxic chemotherapy for ALL combines multiple antileukemic drugs in various combinations. Chemotherapy for ALL consists of three phases: **remission induction, intensification, and maintenance therapy.**

Phase	**Description**	**Agents**
Remission induction	The aim of remission induction is to rapidly kill most tumor cells and get the patient into remission. This is defined as the presence of less than 5% leukemic blasts in the bone marrow, normal blood cells and absence of tumor cells from blood, and absence of other signs and symptoms of the disease. Central nervous system (CNS)	Combination of prednisolone or dexamethasone, vincristine, asparaginase (better tolerance in pediatric patients), and daunorubicin(used in Adult ALL) is used to induce remission. Central nervous system prophylaxis can be achieved via irradiation, cytarabine + methotrexate, or

	prophylaxis should begin during this phase of treatment and continue during the consolidation/intensification period. The rationale is based on the presence of CNS involvement in 10%-40% of adult patients at diagnosis.	liposomal cytarabine. In Philadelphia chromosome-positive ALL, the intensity of initial induction treatment may be less than has been traditionally given
Consolidation/intensification	Intensification uses high doses of intravenous multidrug chemotherapy to further reduce tumor burden. Since ALL cells sometimes penetrate the CNS, most protocols include delivery of chemotherapy into the CNS fluid (termed intrathecal chemotherapy). Some centers deliver the drug through Ommaya reservoir (a device surgically placed under the scalp and used to deliver drugs to the CNS fluid and to extract CNS fluid for various tests). Other centers would perform multiple lumbar punctures as needed for testing and treatment delivery.	Typical intensification protocols use vincristine, cyclophosphamide, cytarabine, daunorubicin, etoposide, thioguanine or mercaptopurine given as blocks in different combinations. For CNS protection, intrathecal methotrexate or cytarabine is usually used combined with or without cranio-spinal irradiation (the use of radiation therapy to the head and spine). Central nervous system relapse is treated with intrathecal administration of hydrocortisone, methotrexate, and cytarabine.
Maintenance therapy	The aim of maintenance therapy is to kill any residual cell that was not killed by remission induction and intensification regimens. Although such cells are few, they will cause relapse if not eradicated.	For this purpose, daily oral mercaptopurine, once weekly oral methotrexate, once monthly 5-day course of intravenous vincristine and oral corticosteroids are usually used. The length of maintenance therapy is 3 years for boys, 2 years for girls and adults

Chronic Lymphatic Leukemia (CLL)

- CLL is characterized by the progressive accumulation of usually monoclonal, functionally incompetent lymphocytes, mature appearing lymphoid cells.
- Patients with CLL commonly develop complications associated with the intrinsic immune dysfunction that results in immunodeficiency and the development of autoimmune disorders
- Small lymphocytic lymphoma (SLL) is a similar disease with predominate lymph node enlargement.
- CLL and small lymphocytic lymphoma (SLL) are considered part of a spectrum of the same disease.
- Both are characterized by clonal proliferation of mature B-lymphocytes. In SLL, there is more lymph node involvement and less bone marrow and peripheral blood involvement; in CLL, the bone marrow and the peripheral blood are more affected.

- CLL is considered to be identical (ie, one disease with different manifestations) to the mature (peripheral) B cell neoplasm small lymphocytic lymphoma (SLL), one of the indolent non-Hodgkin lymphomas.

EPIDEMIOLOGY

- CLL is the most common leukemia in adults in Western countries, accounting for approximately 25 to 30 percent of all leukemias in the United States.
- The disorder is more common in men, with a male to female ratio of approximately 1.3:1 to 1.7:1.
- CLL is considered to be mainly a disease of older adults, with a median age at diagnosis of approximately 70 years; however, it is not unusual to make this diagnosis in younger individuals from 30 to 39 years of age.
- Genetic rather than environmental factors are the most likely explanation for these differences.

CLINICAL PRESENTATION

- The clinical presentation of CLL or SLL relate to tissue infiltration (lymphadenopathy, organomegaly), peripheral blood cytopenia (anemia, bleeding, infections), or immune suppression (infections and malignancies) and autoimmune phenomenon (hemolytic anemia).
- **Most patients feel entirely well with no symptoms when a routine blood count reveals an absolute lymphocytosis, leading to a diagnosis of CLL.**
- 5 to 10 % of patients present with the typical "B" symptoms of lymphoma which include one or more of the following:
    - Unintentional weight loss ≥10 percent of body weight within the previous six months.
    - Fevers of >100.5˚F (>38˚C) for ≥2 weeks without evidence of infection.
    - Drenching night sweats without evidence of infection.
    - Extreme fatigue (ie, ECOG Performance status 2 or worse; cannot work or unable to perform usual activities)

Signs

- Lymphadenopathy
    - The most common abnormal finding on physical examination of the patient with CLL is lymphadenopathy, present in 50 to 90 percent of patients among various series.
    - Lymph node enlargement may be generalized or localized, and individual lymph nodes can vary greatly in size.
    - The most commonly affected sites are cervical, supraclavicular, and axillary.
    - Characteristically, enlarged nodes in CLL are firm, rounded, discrete, nontender, and freely mobile upon palpation. Exceptions to these generalizations are encountered, particularly **when the nodes have grown rapidly.**
    - Occasionally, several enlarged nodes in the same anatomical site (eg, cervical triangle, axilla or femoral-inguinal areas) may become confluent, forming large spherical lymphoid masses.

- In addition, new lymph nodes may appear in places other than the usual lymph node-bearing sites, such as over the sacrum or the thorax.

Splenomegaly

- The spleen is the second most frequently enlarged lymphoid organ, being palpably enlarged in 25 to 55 percent of cases.
- As is the case with enlarged lymph nodes, an enlarged spleen in CLL is usually **painless and nontender to palpation**, with a sharp edge and a smooth firm surface. Painful and infarcted splenic enlargement is an unusual presenting feature.

Hepatomegaly

- Enlargement of the liver may be noted at the time of initial diagnosis in 15 to 25 percent of cases.
- The liver is usually only mildly enlarged, ranging from 2 to 6 cm below the right costal margin, with a span of dullness to percussion of approximately 10 to 16 cm.
- Upon palpation, the liver is usually nontender and firm with a smooth surface.

Skin

- Infiltration with CLL cells may occur in any organ, but, at the time of diagnosis, the skin (leukemia cutis) is the most commonly involved non-lymphoid organ.
- These lesions most commonly involve the face and can manifest as macules, papules, plaques, nodules, ulcers, or blisters. Diagnosis is made based upon biopsy of the involved skin.

DIAGNOSIS

- The diagnosis of CLL should be strongly considered in **patients** with absolute lymphocyte count above **5000/ µL.** However, confirmation requires review of peripheral blood smear morphology by hematologist or pathologist
- Definitive diagnosis of CLL requires the presence of the following three parameters.
  - Absolute lymphocytosis defined as lymphocyte count more than 5000 cells/µl.
  - Confirming the presence of excess mature appearing lymphocytes on the peripheral blood smear.
  - Immunophenotyping (Flow cytometry) from peripheral blood: to confirm the presence B-cell markers on the neoplastic lymphoid cells and their clonality.

LABORATORY ABNORMALITIES.

Lymphocytosis

- the most noteworthy laboratory abnormality found in CLL is lymphocytosis in the peripheral blood and bone marrow.

  - Although the absolute blood lymphocyte threshold for diagnosing CLL has been placed at >5000/microL [5 x 10^9/L] B lymphocytes, a significant proportion of patients present with counts as high as 100,000/microL [100 x 10^9/L].
- **Cytopenias**
  - Neutropenia, anemia, and thrombocytopenia may be observed at the time of initial diagnosis, and are usually not severe.
  - These can be related to autoimmune hemolytic anemia, pure red cell aplasia, autoimmune thrombocytopenia, or agranulocytosis.
- Patients with CLL have an increased incidence of autoimmune hemolytic anemia (AIHA). The direct antiglobulin (Coombs) test (DAT) may be positive at some time during the course of the disease in up to 35 percent of cases; overt AIHA occurs in 11 percent of cases.
- **Other abnormal findings** – There are no characteristic abnormalities in blood chemistry, but elevated levels of serum lactate dehydrogenase (LDH) and beta-2 microglobulin were found in approximately 60 percent in one series of patients with progressive or advanced CLL entering a therapeutic trial. Elevations of uric acid, hepatic enzymes (ALT or AST) and, rarely, calcium may also be observed.

PATHOLOGIC FEATURES

- **Morphology**
  - The peripheral blood smear of patients with CLL demonstrates a lymphocytosis.
  - The leukemic cells are typically small, mature appearing lymphocytes with a dense nucleus, partially aggregated (clumped) chromatin, and without discernible nucleoli.
  - There is a narrow border of clear to slightly basophilic cytoplasm.
- **Immunophenotype**
  - Immunophenotypic analysis, usually by flow cytometry, is a key component to the diagnosis of CLL. There are three major characteristic immunophenotypic findings:
    - Expression of **B cell** associated antigens including **CD19, CD20, and CD23**. Expression of CD20 is usually weak. Expression of CD21 and CD24 can be seen, but is not required for diagnosis.
    - Expression of **CD5**, an antigen commonly expressed by **T cells.**
    - Low levels of surface membrane immunoglobulin (ie, SmIg weak). The immunoglobulin is most often **IgM or both IgM and IgD**, and only a single immunoglobulin light chain is expressed (ie, either kappa or lambda but not both), confirming the clonal nature of these cells. In rare cases, several Ig clones may coexist.
- **Bone marrow aspirate and biopsy**
  - Bone marrow aspirate and biopsy are not required for the diagnosis of CLL.
  - If bone marrow biopsy and aspiration are performed at the time of initial diagnosis, they usually demonstrate normal to increased cellularity, with lymphocytes accounting for >30 percent of all nucleated cells.

- **Lymph node biopsy**
  - CLL and small lymphocytic lymphoma (SLL) are considered to be the same disease with different clinically manifestations.
  - Historically, the diagnosis of SLL was made via a lymph node biopsy in a patient presenting with lymphadenopathy but without peripheral lymphocytosis, while CLL was diagnosed through examination of the peripheral blood and bone marrow in patients with lymphocytosis.
  - Currently, the diagnosis of SLL is reserved for patients demonstrating lymph node pathology consistent with CLL/SLL but with an absolute peripheral clonal lymphocyte count that does not exceed 5000/microL [5 x 10^9/L] and no evidence of neutropenia, anemia, or thrombocytopenia related to the disease.

Rai staging system

- The Rai system is based upon the concept that in CLL there is a gradual and progressive increase in the body burden of leukemic lymphocytes, starting in the blood and bone marrow (lymphocytosis), progressively involving lymph nodes (lymphadenopathy), spleen and liver (organomegaly), with eventual compromise of bone marrow function (anemia and thrombocytopenia).
- Stage 0 (lymphocytosis) — 25 percent
- Stages I to II (lymphadenopathy, organomegaly) — 50 percent
- Stages III to IV (anemia, thrombocytopenia) — 25 percent
- In the original series describing the Rai system, the median survival from the time of diagnosis according to stage was:
  - Stage 0 — 150 months
  - Stage I — 101 months
  - Stage II — 71 months
  - Stages III and IV — 19 months

Binet staging system

- The Binet staging system takes into consideration five potential sites of involvement: cervical, axillary, and inguinal lymph nodes (whether unilateral or bilateral, each area is counted as one), spleen, and liver. Involvement is judged only by physical exam and does not take into consideration the results of imaging studies for staging purposes.
- Patients are classified according to the number of involved sites plus the presence of anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/microL).
- Stage A — Fewer than three involved lymphoid sites
- Stage B — Three or more involved lymphoid sites
- Stage C — Presence of anemia and/or thrombocytopenia
- While survival by stage has improved with the evolution of treatment since this publication, median survival for the prognostic groups studied by Binet was:
  - Stage A — Comparable to age-matched controls
  - Stage B — 84 months

- Stage C — 24 months

Treatment options

- Treatment should be decided and provided by a hematologist.
  1. Wait and watch with no treatment: for asymptomatic patients
  2. Combination chemotherapy
  3. Targeted therapies
  4. Monoclonal antibody therapies
- **Indications for treatment**
  - Symptomatic disease: B-symptoms, bulky lymph node or splenomegaly > 6cm
  - below the left costal margin.
  - Anemia
  - Thrombocytopenia

14.2 Lymphomas

- Lymphomas are neoplastic transformation of the cells of lymphoid tissues. The origins could be in nodal sites (lymph nodes) or extra-nodal sites e.g. GI, CNS.
- There are dozens of subtypes of lymphomas. The two main categories of lymphomas are Hodgkin's lymphomas (HL) and the non-Hodgkin lymphomas (NHL).
- WHO includes two other categories as types of lymphoma: multiple myeloma and immunoproliferative diseases.
- About 90% of lymphomas are non-Hodgkin lymphomas.
- Lymphomas and leukemia's are a part of the broader group of tumors of the hematopoietic and lymphoid tissues.

Hodgkin's lymphoma (HL)

- HL, formerly called Hodgkin's disease, arises from germinal center or post-germinal center B cells.
- HL has a unique cellular composition, containing a minority of neoplastic cells **(Reed-Sternberg cells and their variants)** in an inflammatory background.
- It is separated from the other B cell lymphomas based on its unique clinicopathologic features, and can be divided into two major sub-groups, based on the appearance and immunophenotype of the tumor cells.
- **Hodgkin 's lymphoma** is a distinct group of lymphomas with few histologic sub-types.
- It predominately involves lymph nodes; extra-nodal involvement is not common.
- It progresses from one lymph node region to other in fairly predictable fashion.
- **Classical HL**

- The tumor cells in this group are derived from germinal center B cells, but typically fail to express many of the genes and gene products that define normal germinal center B cells. Based on differences in the appearance of the tumor cells and the composition of the reactive background, classical HL is further divided into the following subtypes:
  - Nodular sclerosis classical HL (NSHL)
  - Mixed cellularity classical HL (MCHL)
  - Lymphocyte rich classical HL (LRHL)
  - Lymphocyte depleted classical HL (LDHL)
- **Nodular lymphocyte predominant HL** — The tumor cells in this subtype retain the immunophenotypic features of germinal center B cells.

EPIDEMIOLOGY

- Represents ~10% of all cases of malignant lymphoma. Typically affects young adults Presents with painless lymphadenopathy involving the neck and chest; systemic symptoms are common.
- HL has a bimodal age distribution curve. The pattern of age-specific incidence differs by geographic location and appears to parallel the level of industrial development: In the US and other economically advantaged countries, there is one peak in young adults (approximately age 20 years) and one in adults of older age (approximately age 65 years); the majority of patients are young adults.
- In the US and Europe, the approximate percentage of classic HL cases from each subgroup are as follows:
  - Nodular sclerosis classical HL (70 percent)
  - Mixed cellularity classical HL (20 to 25 percent)
  - Lymphocyte rich classical HL (5 percent)
  - Lymphocyte depleted classical HL (less than 1 percent)

Risk factors

- **Socioeconomic status and the environment**
  - In economically advantaged countries, the risk of developing HL as a young adult is consistently associated with factors indicative of a high standard of living in early childhood, including single family housing and small family size.
  - These associations appear to be specific for the nodular sclerosis subtype of HL and for disease occurring from early childhood through middle adulthood.
- **Immunosuppression**
  - the incidence of HL is increased in a number of settings associated with immunodeficiency, including solid organ or hematopoietic cell transplantation, therapy with immunosuppressive drugs (e.g, in patients with autoimmune disease), and HIV infection.

- **Autoimmune disorders**
  - Patients with a history of autoimmune disorders are at increased risk for the development of HL and can pose challenging management issues due to comorbidities and late treatment related toxicities.
  - A personal history of rheumatoid arthritis, SLE or sarcoidosis
  - A family history of sarcoidosis or ulcerative colitis
- **EBV infection**
  - Incidence of HL is high among pts with history of EBV.
  - The risk of EBV positive pts are four times; latency period is 4 years.

CLINICAL PRESENTATION

- Non tender lymphadenopathy central pattern, 70 - 80 % left supraclavicular and mediastinal B symptoms
  - Common in patients with advanced stage disease.
- Pruritis, typically is not associated with a rash
- Intense pain in the sites of disease upon alcohol ingestion
- Obstructive symptoms
- Fluid collections in the third space
- Organomegally
- **The clinical presentation also varies according to the histologic subtype of classic HL NS**
  - Accounts for 70% of cases in the Western world.
  - Mediastinal involvement is common
  - Males and females are affected in equal proportion
  - Most patients are between the ages of 15 and 35 years.
- **Mixed cellularity**
  - The second-most-common subtype in the industrial world, representing 20% of cHL.
  - The median age of presentation is 38
  - Males are affected more commonly.
  - Patients typically present with peripheral lymphadenopathy
  - Splenic involvement occurs in 30%
  - Advanced at the time of presentation
  - Associated with a poorer prognosis than NS.
- **LR cHL**
  - Early stage disease
  - Peripheral nodes
  - Patients are older 43 years
- **LD cHL**
  - Is the least common subtype
  - It is more common in the industrial world and in HIV-infected individuals
  - The median age of onset is in the 30
  - Males are more often affected

  - Extra nodal and intra-abdominal disease commonly is seen
  - Advanced stage disease and systemic symptoms are common
- **Bone marrow involvement 50%**
  - Has the worst prognosis
  - Extra nodal and intra-abdominal disease commonly is seen
  - Advanced stage disease and systemic symptoms are common.
- **Spleen involvement in CHL**
  - In pt with LAP below the diaphragm
  - Systemic symptoms
  - MC
  - Can occur without splenomegaly
  - Splenomegaly can be found without tumor involvement

Diagnosis

- **LN biopsy** is diagnostic
  - RSC with surrounding inflammatory cells
  - RSC not specific for HL
- **Immunostaining**
  - Confirm the diagnosis of HL
  - cHL is positive for
    - CD 30 in all cases
    - CD 15 in 85 %
    - CD 20 in 20%
    - Negative CD 45
- **Lab features**; No diagnostic lab features
  - CBC; anemia, thrombocytopenia, lymphopenia
  - ESR elevated
  - LFT increased
  - LDH and , uric acid will be elevated
  - Serum albumin will be low
  - B2 microglobuline high
  - HIV test
- Imaging
  - CXR, CT, PET
  - Cardiac evaluation and pulmonary function tests
  - BM biopsy for staging, can be deferred in most patients

STAGING

- Main determinant of prognosis and treatment
- The Ann Arbor staging system has been employed in HL for more than 25 years.

- The Ann Arbor staging system with Cotswolds modifications is the current staging system
- **There are four stages**
  - **Stage I** – Involvement of a single lymph node region (I) or of a single extra lymphatic organ or site (IE).
  - **Stage II** – Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE).
    - The number of anatomic regions should be indicated by a subscript (eg, II-3).
  - **Stage III** – Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm (III) which may include the spleen (IIIS) or limited, a contiguous extralymphatic organ or site (IIIE) or both (IIIES).
    - Subdivided into stage III-1 or III-2:
    - Stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac or portal nodes
    - Stage III-2 is used for patients with involvement of the paraaortic, iliac, inguinal, or mesenteric
  - **Stage IV** – Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement.
- **N.B,** all cases are sub classified to indicate the absence (A) or presence (B) of one or more of the following three systemic symptoms
- significant **unexplained fever**, **night sweats**, or **unexplained weight loss** exceeding 10 percent of body weight **during the six months prior to diagnosis.**

Treatment

- Depends on the stage of the disease and the presence of adverse prognostic factors.
- Treatment group includes
  - Early stage favorable and unfavorable
  - Advanced stage
- Treatment of early stage HL
- Early stage Includes CS I and II;Further classified in to two
  - Early stage favorable; no risk factors
  - Early stage unfavorable; one or more risk factors
- Risk factors in early stage Hodgkin lymphoma. A number of prognostic indicators have been identified in early stage cHL
- **The GHSG scale includes five risk factors**
  - Bulky mediastinal disease
  - ESR of ≥30 in the presence of B symptoms or ≥50 without B symptoms
  - Extranodal extension of disease
  - Three or more lymph node sites of involvement.

- **The EORTC scale includes**
    - Age ≥50 years
    - Bulky mediastinal disease
    - ESR of ≥30 in the presence of B symptoms or ≥50 without B symptom
    - Four or more nodal sites of involvement
- Therapeutic options include combined modality therapy:
- Early Favorable disease
    - Two to four cycles of **ABVD** plus **IFRT 20- 30 GY**
    - Stanford V for 8 weeks plus 30 GY IFRT to sites > 5cm
- Early unfavorable disease non bulky disease
    - Four cycles of **ABVD plus 30 GY IFRT**
    - Two cycles of escalated **BEACOPP** plus two cycles of **ABVD plus 30 GY IFRT**
- For patients with bulky disease
    - 4 to 6 cycles of **ABVD** or stanford V followed by **36 GY IFRT**

Treatment of advanced stage HL

- Advanced stage includes- CS III and CS IV
- Options of treatment
    - ABVD 6 cycles
    - Stanford V with IFRT
    - Escalated BEACOPP
- NB; **ABVD**=Adriamycin(doxorubicin), Bleomycin, Vinblastin, Dacarbazin
- **BEACOPP**
    - **(escalated)=**Bleomycin,Etoposide,Adriamycin,**cyclophosphamide,oncovin(vincristin),procarbazin,Prednisone,G-csf.**
- **International Prognostic Score in advanced-stage HL.**
    - Age >45 years
    - Male
    - WBC >15,000/mm3
    - Hgb <10.5 g/dl
    - Absolute lymphocyte count <600/mm3 or <8% of WBC
    - Albumin <4.0 g/dl
    - Stage IV disease.

Non Hodkins lymphoma

- Non-Hodgkin's lymphoma (NHL) is a broader category which includes a significantly
- heterogenous lymphoma with variable clinical, histologic, genetic abnormalities,
- outcome and treatment characteristics.it consists of a diverse group of malignant neoplasms variously derived from B cell progenitors, T cell

progenitors, mature B cells, mature T cells, or (rarely) natural killer cells; generally all malignancies of the lymphoid system with the exception of HL.

- The vast majority of NHLS are B-cell in origin.

Epidemiology

- Incidence of NHL has been increasing steadily in North America and other industrial countries with a doubling of cases between 1970 and 1990 and stabilization thereafter.
- Fifth most common ca in USA — 4.2% of all cases of ca
  - Mean age at Dx 45- 55 years
  - More common in male
  - Higher in whites than blacks
- *Risk factors*
  - **Infection;** EBV, HTLV-I, HHV-8, HCV, H. Pylori, Chlamydia psittaci, Campylobacter jejuni, Borrelia burgdorferi
  - **Occupational exposure to certain pesticides and herbicides**
  - **Drugs**
  - **Congenital disease;** ataxia-telangiectasia, Wiskott-Aldrich syndrome.
  - **Acquired**; Immunosuppression associated with HIV infection,Iatrogenically induced immune suppression in the organ transplantation setting,Autoimmune disorders :- rheumatoid arthritis, Sjögren syndrome, and Hashimoto thyroiditis, IBD, SLE;HL.

CLINICAL PRESENTATION

- The clinical presentation of NHL varies tremendously depending upon the type of lymphoma and the areas of involvement. Some NHLs behave indolently with lymphadenopathy waxing and waning over years. Others are highly aggressive, resulting in death within weeks if left untreated. In typical cases:
- **Aggressive lymphomas** commonly present acutely or subacutely with a rapidly growing mass, systemic B symptoms (ie, fever, night sweats, weight loss), and/or elevated levels of serum lactate dehydrogenase and uric acid. Examples of lymphomas with this aggressive or highly aggressive presentation include **diffuse large B cell lymphoma, Burkitt lymphoma, adult T cell leukemia-lymphoma, and precursor B and T lymphoblastic leukemia/lymphoma.**
- **Indolent lymphomas** are often insidious, presenting only with slow growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenias. Examples of lymphomas that typically have indolent presentations include follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and splenic marginal zone lymphoma.
- The natural history of these tumors shows significant patient-to-patient variability.

- Less common presentations include skin rash, pruritus, exaggerated (hypersensitivity) reactions to insect stings or bites, generalized fatigue, malaise, fever of unknown origin, ascites, and effusions.
- Approximately 50 percent of patients develop extranodal disease (secondary extranodal disease) during the course of their disease, while between 10 and 35 percent of patients have primary extranodal lymphoma at diagnosis. The initial presentation may reflect involvement of extranodal tissues, as follows:
- **Patients with primary gastrointestinal (GI) tract** lymphoma may present with anorexia, weight loss, nausea and vomiting, chronic pain, abdominal fullness, early satiety, symptoms associated with visceral obstruction, or even acute perforation and GI hemorrhage. Occasional patients will present with malabsorption syndrome.
- **Patients with primary CNS lymphoma** may present with headache, lethargy, focal neurologic symptoms, seizures, paralysis, spinal cord compression (0.1 to 6.5 percent of patients), or lymphomatous meningitis.

Oncologic emergencies

- Potentially emergent complications of NHL need to be considered during the initial workup and evaluation.
- Prompt recognition and therapy is critical for these situations, which may be life-threatening and/or interfere with and delay treatment of the underlying NHL
- These can include:
    - Spinal cord compression
    - Pericardial tamponade
    - Hypercalcemia (eg, adult T cell leukemia-lymphoma)
    - Superior or inferior vena cava obstruction
    - Hyperleukocytosis (eg, B or T cell lymphoblastic leukemia/lymphoma)
    - Acute airway obstruction (eg, mediastinal lymphoma)
    - Lymphomatous meningitis and/or CNS mass lesions
    - Hyperuricemia and tumor lysis syndrome
    - Hyperviscosity syndrome (eg, lymphoplasmacytic lymphoma with Waldenstrom macroglobulinemia)
    - Intestinal obstruction, intussusception
    - Ureteral obstruction, unilateral or bilateral hydronephrosis
    - Severe hepatic dysfunction
    - Venous thromboembolic disease
    - Severe autoimmune hemolytic anemia and/or thrombocytopenia (eg, small lymphocytic lymphoma

- If patients with NHL develop angioedema, they may have an acquired form of C1 inhibitor deficiency that requires emergent treatment with infused C1 inhibitor concentrates

- **Systemic complaints (B symptoms)** – Up to 40 percent of patients with NHL present with systemic complaints of fever, weight loss, or night sweats (ie, B symptoms). These complaints are of importance in determining prognosis, and have been formally defined as follows:
    - Fever — Temperature >38°C (>100.4°F)
    - Weight loss — Unexplained loss of >10 percent of body weight over the past six months
    - Sweats — The presence of drenching night sweats
- **Lymphadenopathy** – More than two-thirds of patients with NHL present with peripheral lymphadenopathy that is generally painless.
- **Fever of unknown origin;** NHL, especially one of the aggressive or highly aggressive variants, is a common cause of FUO due to malignancy.
- **Hepatosplenomegaly**

DIAGNOSIS and Investigations

- The diagnosis lymphoma needs **lymph node biopsy**. FNAC is not enough
- Once a diagnosis of lymphoma is made further investigations are needed for staging, prognosis, and for treatment purposes.
- CBC
- Uric acid level
- LDH
- LFT
- BUN and Creatinine
- Hepatitis B and C virus serologies, HIV screening
- Staging investigations: Chest x-ray, abdominal ultrasound or CT-scan, bone aspiration or biopsy

TREATMENT

- Indolent
    - Potential cure only through HSCT (Hematopoietic stem cell transplantation).
    - Watchful waiting early on for some patients
    - Chemotherapy/immunotherapy/radiotherapy/ combination with indication
- Aggressive
    - Chemotherapy as soon as the dx is established
    - Radiotherapy for the right indications
    - HSCT
- Highly aggressive
    - Highly chemo sensitive. SO, Chemotherapy ASAP
- **NB;** The most common chemotherapy used for non-Hodgkin lymphoma is **CHOP-R.** (C-cyclophosphamide, H-hydroxydaunorubicin, O-oncovin, P-prednisone, R-rituximab)

Special considerations

1) Tumor lysis syndrome (TLS)

- **It** is an oncologic emergency that is caused by massive tumor cell lysis with the release of large amounts of **potassium, phosphate, and nucleic acids** into the systemic circulation.
- Catabolism of the nucleic acids to uric acid leads to hyperuricemia, and the marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and can also induce renal vasoconstriction, impaired autoregulation, decreased renal blood flow, and inflammation, resulting in acute kidney injury.
- Hyperphosphatemia with calcium phosphate deposition in the renal tubules can also cause acute kidney injury.
- TLS most often occurs after the initiation of cytotoxic therapy in patients with high-grade lymphomas (**particularly the Burkitt subtype**) and **acute lymphoblastic leukemia.** However, TLS can occur spontaneously and with other tumor types that have a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.

PATHOGENESIS

- In the setting of a malignancy with a high proliferative rate, large tumor burden, and/or a high sensitivity to treatment, initiation of cytotoxic chemotherapy, cytolytic antibody therapy, radiation therapy, or sometimes glucocorticoid therapy alone can result in the rapid lysis of tumor cells.
- This releases massive quantities of intracellular contents (potassium, phosphate, and nucleic acids that can be metabolized to uric acid) into the systemic circulation. The metabolic consequences include;
    - **Hyperkalemia**
    - **Hyperphosphatemia**
        - The phosphorus concentration in malignant cells is up to four times higher than in normal cells. Thus, rapid tumor breakdown often leads to hyperphosphatemia, which can cause secondary hypocalcemia.
        - When the calcium concentration times phosphate concentration (the calcium phosphate product) exceeds 60 mg^2/dL^2, there is an increased risk of calcium phosphate precipitation in the renal tubules, which can lead to acute kidney injury.
        - In addition, precipitation in the heart may lead to cardiac arrhythmias. Renal replacement therapy may be needed if the calcium phosphate product is ≥70 mg^2/dL^2.

- **secondary hypocalcemia**
- **hyperuricemia**
  - Hyperuricemia is a consequence of the catabolism of purine nucleic acids to hypoxanthine and xanthine, and then to uric acid via the enzyme xanthine oxidase
- **acute kidney injury**.

Xanthinuria

- Allopurinol blocks the catabolism of hypoxanthine and xanthine, leading to an increase in the levels of these metabolites.
- Xanthine is much less soluble than uric acid, and urinary alkalinization increases the solubility of xanthine much less than the solubility of uric acid because the pKa is much higher for xanthine
- Thus, patients with massive TLS who are receiving allopurinol are at risk for xanthine precipitation in the tubules, resulting in xanthine nephropathy or xanthine stone formation.
- Because the serum xanthine level is not routinely measured, its effect on the risk of acute kidney injury is not certain. In contrast to the effect of allopurinol, xanthine concentration is not increased by rasburicase (recombinant urate oxidase), which is now preferred in most patients at high risk for TLS. Rasburicase promotes the degradation of uric acid to the much more water-soluble compound allantoin.
- However, in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, hydrogen peroxide, a breakdown product of uric acid, can cause methemoglobinemia and, in severe cases, hemolytic anemia. For this reason, rasburicase is contraindicated in patients with G6PD deficiency.

CLINICAL MANIFESTATIONS

- The symptoms associated with tumor lysis syndrome (TLS) largely reflect the associated metabolic abnormalities (hyperkalemia, hyperphosphatemia, and hypocalcemia).
- They include nausea, vomiting, diarrhea, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death.
- **Cairo-Bishop definition** – The Cairo-Bishop definition, proposed in 2004, provided specific laboratory criteria for the diagnosis of TLS both at presentation and within seven days of treatment. It also incorporated a grading system to help delineate the degree of severity of TLS.
- **Laboratory TLS** was defined as any two or more abnormal serum values (hyperuricemia,hyperkalemia,hyperphosphatemia and hypocalcemia), present within three days before or seven days after instituting chemotherapy in the setting of adequate hydration (with or without alkalinization) and use of a hypouricemic agent.

- **Clinical TLS** was defined as laboratory TLS plus one or more of the following that was not directly or probably attributable to a therapeutic agent: increased serum creatinine concentration (≥1.5 times the upper limit of normal [ULN]), cardiac arrhythmia/sudden death, or a seizure.

RISK STRATIFICATION

High risk

- Included in the high-risk group (>5 percent risk of TLS) are:
- **All Burkitt leukemia**, stage III or IV Burkitt lymphoma or early stage Burkitt lymphoma with serum LDH level two or more times the upper limit of normal (≥2X ULN)
- Other acute lymphoblastic leukemia **(ALL)** with a white blood cell (WBC) count ≥100,000 per microL and/or serum lactate dehydrogenase (LDH) level ≥2X ULN
- **AML with WBC count ≥100,000 per microL**
- Stage III or IV lymphoblastic lymphoma or early stage lymphoblastic lymphoma with serum LDH level two or more times the upper limit of normal (≥2X ULN)
- Chronic lymphocytic leukemia (CLL) treated with venetoclax and lymph node ≥10 cm or lymph nodes ≥5 cm plus absolute lymphocyte count ≥25 x 10^9/L, **and** elevated serum uric acid level
- Adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma with serum LDH level above the ULN **and** a bulky tumor mass
- Stage III or IV childhood diffuse large B-cell lymphoma with serum LDH level ≥2X ULN
- Patients with intermediate-risk disease (see below) with renal dysfunction and/or renal involvement or uric acid, potassium, or phosphate levels above the ULN

Intermediate risk

- The intermediate-risk group (risk of TLS 1 to 5 percent) includes:
- Adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma with serum LDH level above ULN but **without** bulky disease
- Stage III or IV childhood anaplastic large cell lymphoma with serum LDH level <2X ULN
- Stage III or IV childhood diffuse large B-cell lymphoma with serum LDH level ≥2X ULN
- Early stage Burkitt lymphoma with serum LDH level <2X ULN
- ALL with WBC <100,000/microL and serum LDH level <2X ULN
- AML with WBC 25,000 to 100,000/microL or AML with WBC<25,000/microL and LDH ≥ 2X ULN
- Early stage lymphoblastic lymphoma with serum LDH level <2X ULN

- CLL/small lymphocytic lymphoma (SLL) treated with fludarabine, rituximab, or lenalidomide, or venetoclax with lymph nodes ≥5 cm **or** an absolute lymphocyte count ≥25 x 10^9/L, and/or those with a high WBC count (≥50,000/microL)
- Rare bulky solid tumors that are highly sensitive to chemotherapy (such as neuroblastoma, germ cell cancer, small cell lung cancer)

Low risk – Patients at low risk for TLS (<1 percent risk) include [16]:

- AML with WBC count <25,000/microL and serum LDH level <2X ULN
- CLL/SLL with a WBC count ≤50,000/microL and not treated with fludarabine/rituximab or venetoclax
- Multiple myeloma and chronic myelogenous leukemia (CML)
- Other adult non-Hodgkin lymphomas (NHL) that do not meet the criteria for high risk or intermediate risk, with serum LDH level within normal limits
- Other solid tumors

Prevention and treatment

- **PREVENTION;** The main prophylactic strategies are intravenous (IV) hydration and the use of hypouricemic agents, such as allopurinol and rasburicase.
- **IV hydration** – Aggressive IV hydration is the cornerstone of preventing TLS and is recommended prior to therapy in all patients at intermediate or high risk for TLS.The goal of IV hydration is to improve renal perfusion and glomerular filtration, and induce a high urine output to minimize the likelihood of uric acid or calcium phosphate precipitation in the tubules.
- **Urinary alkalinization** – The role of urinary alkalinization with either acetazolamide and/or sodium bicarbonate is unclear and controversial. In the past, alkalinization to a urine pH of 6.5 to 7 or even higher was recommended to increase uric acid solubility, thereby diminishing the likelihood of uric acid precipitation in the tubules
- **Allopurinol** – For the initial management of adult and pediatric patients at intermediate risk for TLS we suggest allopurinol rather than rasburicase, as long as pretreatment uric acid levels are not elevated (ie, <8 mg/dL [476 micromol/L]), although administration of a single dose of rasburicase is a reasonable alternative in this setting.
- Allopurinol is a hypoxanthine analog that competitively inhibits xanthine oxidase, blocking the metabolism of hypoxanthine and xanthine to uric acid.
- **Rasburicase** – For the initial management of most pediatric and adult patients at high risk for TLS, especially those with impaired renal or cardiac function, we recommend rasburicase rather than allopurinol.
- An alternative approach to allopurinol for lowering serum uric acid levels is to promote the degradation of uric acid by the administration of urate oxidase (uricase), which catalyzes oxidation of uric acid to the much more water-soluble compound allantoin.

TREATMENT OF ESTABLISHED TLS

- **Electrolyte abnormalities…**manage accordingly
- **Renal replacement therapy-** Among the indications for renal replacement therapy in patients with TLS are
    - Severe oliguria or anuria
    - Intractable fluid overload
    - Persistent hyperkalemia
    - Hyperphosphatemia-induced symptomatic hypocalcemia
    - A calcium-phosphate product ≥70 mg^2/dL^2

2) Hyperleukocytosis and leukostasis in hematologic malignancies

- **Hyperleukocytosis** refers to a laboratory abnormality that has been variably defined as a total leukemia blood cell count greater than **50 x 10^9/L (50,000/microL) or 100 x 10^9/L (100,000/microL).** In contrast, leukostasis (also called symptomatic hyperleukocytosis) is a medical emergency most commonly seen in patients with acute myeloid leukemia or chronic myeloid leukemia in blast crisis. It is characterized by an extremely elevated blast cell count and symptoms of decreased tissue perfusion.
- **Leukostasis** is a pathologic diagnosis in which white cell plugs are seen in the microvasculature. Clinically, leukostasis is typically diagnosed empirically when a patient with leukemia and hyperleukocytosis presents with respiratory or neurological distress. Prompt treatment is indicated since, if left untreated, the one-week mortality rate is approximately 20 to 40 percent.

EPIDEMIOLOGY

- The incidence of hyperleukocytosis and leukostasis vary by leukemia type and patient population. In general, symptoms of leukostasis are more common in leukemias with large, poorly deformable blasts, such as acute myeloid leukemia.
- **Acute myeloid leukemia** — Hyperleukocytosis is present in **10 to 20 percent** of patients with newly diagnosed acute myeloid leukemia (AML). Symptoms of leukostasis occur less frequently and typically affect patients with white blood cell (WBC) counts over 100 x 10^9/L (100,000/microL).
- **Acute lymphoblastic leukemia** — Hyperleukocytosis is seen in **10 to 30 percent** of patients with newly diagnosed acute lymphoblastic leukemia (ALL). Symptoms of leukostasis occur less frequently and typically affect patients with white blood cell (WBC) counts over 100 x 10^9/L (100,000/microL).Tumor lysis syndrome and disseminated intravascular coagulation are more common complications related to the elevated WBC count.
- **Chronic lymphocytic leukemia** — A significant proportion of patients with chronic lymphocytic leukemia (CLL) present with hyperleukocytosis. Symptoms

of leukostasis are rare unless the WBC count exceeds 400 x 10^9/L (400,000/microL).

- **Chronic myeloid leukemia** — Patients with chronic myeloid leukemia (CML) typically present with leukocytosis and a median WBC count of approximately 100 x 10^9/L (100,000/microL). Most often, these are segmented neutrophils, metamyelocytes, and myelocytes. Symptoms of leukostasis are very uncommon in patients in chronic phase but can be seen occasionally in patients with myeloid blast crisis and very elevated blast counts.

SIGNS AND SYMPTOMS

- Although pathologic evidence of leukostasis can be found in most organs in patients with extremely high white blood cell (WBC) counts, the main clinical symptoms of leukostasis and causes of early death are related to involvement of the central nervous system (approximately 40 percent) and lungs (approximately 30 percent).
- **Pulmonary signs and symptoms** include dyspnea and hypoxia with or without diffuse interstitial or alveolar infiltrates on imaging studies. Measurement of the arterial pO2 can be falsely decreased in patients with hyperleukocytosis, since the WBCs in the test tube utilize oxygen. Pulse oximetry provides a more accurate assessment of O2 saturation in this setting.
- **Neurological signs and symptoms** include visual changes, headache, dizziness, tinnitus, gait instability, confusion, somnolence, and, occasionally, coma. In addition, patients who present with hyperleukocytosis have an increased risk of intracranial hemorrhage that persists for at least a week after the reduction of white cell count, perhaps from a reperfusion injury as areas of the brain that were ischemic from leukostasis regain blood flow. Because there can be other structural causes of central nervous system symptoms, brain imaging with **noncontrasted CT or MRI** is indicated in patients with neurologic abnormalities. **Clinicians must be cautious about using intravenous contrast** dye at a time when renal function may be compromised by leukostasis or tumor lysis syndrome, and dehydration.
- Approximately **80 percent** of patients with leukostasis are **febrile,** which may be due to inflammation associated with leukostasis or concurrent infection. Since an infectious cause cannot be easily excluded, we treat empirically for infection in all such patients.
- Less common signs or symptoms of leukostasis include electrocardiographic signs of myocardial ischemia or right ventricular overload, worsening renal insufficiency, priapism, acute limb ischemia, or bowel infarction

DIAGNOSIS

- Leukostasis (symptomatic hyperleukocytosis) is diagnosed empirically when a patient with leukemia and a white blood cell (WBC) count over 100 x 10^9/L (100,000/microL) presents with symptoms thought to be due to tissue hypoxia, most commonly respiratory or neurological distress. The diagnosis requires a high degree of suspicion, and some patients have pathologically proven leukostasis at WBC counts below this level.

- **Pathologically**, leukostasis is diagnosed when a biopsy of involved tissue demonstrates **white cell plugs in the microvasculature** .A pathologic diagnosis of leukostasis is rarely obtained because of the risks associated with biopsy of affected tissues.

MANAGEMENT

- **Cytoreduction** - can be achieved through the use of chemotherapy (hydroxyurea or remission induction chemotherapy) or leukapheresis.
- The initial management of a patient with hyperleukocytosis is directed at rapid lowering of the WBC count.
    - For patients with **symptomatic or asymptomatic** hyperleukocytosis, we suggest initial cytoreduction with **induction chemotherapy** rather than hydroxyurea or leukapheresis.
    - For patients with **asymptomatic** hyperleukocytosis who must have induction chemotherapy **delayed**, we suggest cytoreduction with **hydroxyurea** rather than leukapheresis
    - For patients with **symptoms** of leukostasis who must have induction chemotherapy **delayed,** we suggest initial **leukapheresis** in addition to **hydroxyurea** (if possible) to lower or stabilize the WBC count.
- Supportive care measures:
    - Red blood cell transfusions should be withheld, if possible, until the blast count is reduced. If a transfusion is necessary, it should be administered slowly.
    - Most patients with hyperleukocytosis are candidates for **tumor lysis syndrome** prophylaxis with **aggressive intravenous hydration and allopurinol or rasburicase** to decrease serum uric acid levels.
    - Coagulation abnormalities require aggressive treatment with **platelet transfusions** and **coagulation factors**.

3) Neutropenic fever

- It is the development of fever, often with other signs of infection, in a patient with neutropenia, an abnormally low number of neutrophil granulocytes in the blood.
- **Fever** – Fever in neutropenic patients is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period.
- **Neutropenia** – The definition of neutropenia varies from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 cells/microL, and severe neutropenia is usually defined as an ANC

<500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours.The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration of neutropenia (>7 days). For the purposes of this discussion, **we are defining neutropenia as an ANC <500 cells/microL.**

- **Neutropenic fever syndromes** – A number of neutropenic fever syndromes have been described. The International Immunocompromised Host Society has classified initial neutropenic fever syndromes into the following three categories:
- Microbiologically documented infection — Neutropenic fever with a clinical focus of infection and an associated pathogen
- Clinically documented infection — Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia) but without the isolation of an associated pathogen
- Unexplained fever — Neutropenic fever with neither a clinical focus of infection nor an identified pathogen

- RISK OF SERIOUS COMPLICATIONS
  - The initial clinical evaluation focuses on assessing the risk of serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, intravenous (IV) antibiotics, and prolonged hospitalization.
  - Low-risk patients are defined as those who are expected to be neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days and those with no comorbidities or evidence of significant hepatic or renal dysfunction. Most patients receiving chemotherapy for solid tumors are considered to be low risk for complications requiring hospitalization or prolonging hospitalization.
  - We define high-risk patients as those who are expected to be neutropenic (ANC <500 cells/microL) for >7 days. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk, regardless of the duration of neutropenia.
- **Microbiology and other diagnostic testing;**
  - Stool — If diarrhea is present, send a *Clostridium difficile* toxin assay. There is limited utility in sending stool samples for culture or ova and parasites in hospitalized patients in the United States; these studies can be sent in patients with recent travel to or residence in areas that are endemic for enteric pathogens or if there is another reason to suspect an enteric pathogen.
  - **Urine** — If symptoms of urinary tract infection are present, send urine for bacterial culture and susceptibility testing.
  - **Sk**in — If skin lesions are present, aspirate or biopsy lesions for bacterial and fungal stains and cultures, and, if vesicles are present, send either herpes simplex virus and varicella-zoster virus polymerase

chain reactions (PCRs) or culture plus direct fluorescent antibody testing. When a biopsy is obtained, it should also be sent for histopathology.

- **Respiratory** — If productive cough is present, send sputum for bacterial and fungal stains and cultures and assays for respiratory viruses. Neutropenic patients with pulmonary infiltrates often cannot produce sputum; a more invasive approach, including bronchoscopy with **bronchoalveolar lavage (BAL) or video-assisted thoracoscopic surgery (VATS)**, may need to be pursued in order to make a microbiologic diagnosis. *This may be particularly important for patients with infiltrates on chest radiographs or chest computed tomography (CT) who continue to worsen despite 24 to 48 hours of empiric antibiotic therapy.*
- **Cerebrospinal fluid** — If symptoms of meningitis (fever, headache, nuchal rigidity, altered mental status), are present, send CSF for cell count, glucose, protein, and bacterial culture and susceptibility testing. In addition, in patients with clinical signs of meningitis and/or encephalitis, CSF should also be sent for cryptococcal antigen testing and for PCR testing for herpes simplex virus, cytomegalovirus, varicella-zoster virus, and, in allogeneic hematopoietic cell transplant recipients, human herpes virus 6.
- **Imaging** – Imaging studies should be performed promptly but should not delay initiation of empiric therapy.

APPROACHES TO MANAGEMENT

- Approaches to the management of infection in patients at risk for neutropenic fever include **primary prophylaxis, secondary prophylaxis, empiric therapy, and preemptive therapy.**
- **Primary prophylaxis** – Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk.
- **Secondary prophylaxis** – Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection
- **Empiric therapy** – In patients with chemotherapy-induced neutropenia, empiric therapy involves the initiation of therapy at the time of the onset of neutropenic fever but before a firm diagnosis of infection has been established. ***Empiric antimicrobial therapy is a standard part of the management of neutropenic fever.***
- **Preemptive therapy** – Preemptive therapy involves the initiation of therapy based upon screening with a sensitive microbiology assay (eg, antigen detection or molecular assays) in an attempt to detect the presence of a putative pathogen or early subclinical infection. Patients whose infections are detected using a preemptive approach are treated to avoid progression to invasive disease. ***A preemptive approach is sometimes used for antifungal therapy.***
- The following observations have been made about bacterial infections in neutropenic patients:

- Bacteria are the most frequent infectious causes of neutropenic fever.
- **Gram-negative bacteria (eg, *P. aeruginosa*)** are generally associated with the most serious infections.
- ***S. epidermidis*** is the most common gram-positive pathogen, accounting for approximately one-half of all infections due to gram-positive infections. It is much less virulent than other bacterial pathogens.
- Among gram-positive bacteria, *S. aureus* (particularly methicillin-resistant strains), some viridans streptococci, and enterococci (particularly vancomycin-resistant strains) can cause serious infections. In some European cancer centers, methicillin resistance has dominated among *S. aureus* bloodstream isolates.
- Although anaerobic bacteria are abundant in the alimentary tract, they are infrequent pathogens in patients with neutropenic fever. However, they can contribute to the pathogenesis of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal or pelvic infection, and neutropenic enterocolitis (typhlitis) and can cause anaerobic bacteremia.
- Polymicrobial infections are infrequent, but their frequency appears to be rising
- **Fungal pathogens** – fungal pathogens are common in high-risk patients with neutropenic fever but are uncommon in low-risk patients. *Candida* spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia
- **Viral pathogens** – viral infections, especially human herpesviruses, are common in high-risk patients with chemotherapy-induced neutropenia and are effectively prevented with antiviral prophylaxis.

EMPIRIC THERAPY

- **General principles** – Fever in a neutropenic patient should be considered a medical emergency. Broad-spectrum antibacterials should be given as soon as possible **(within 60 minutes of triage)** and at full doses, adjusted for renal and/or hepatic function. In addition, the diagnostic evaluation should be obtained quickly.
- In high-risk patients, antibiotics should generally be administered intravenously (IV) in a hospital setting.
- Febrile neutropenic patients should be monitored frequently with respect to vital signs (blood pressure, heart rate, respiratory rate, and temperature), performance status (the clinical burden of the neutropenic fever syndrome), and the ability to achieve adequate oral intake in the presence of oral or gastrointestinal mucositis. ***Temporarily holding administration of systemic chemotherapy*** should be considered during the management of the sepsis syndrome until the patient stabilizes. Attention to fluid and electrolyte management is important given the dehydrating effects of fever,

vomiting, and/or diarrhea. ***Urine output of >0.5 mL/kg per hour*** should be maintained.

- the initial therapy of high-risk neutropenic patients with fever;
- Initiation of monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam. Ceftazidime monotherapy has also been shown to be effective and continues to be used at some cancer centers. However, many experts avoid ceftazidime monotherapy because of rising resistance rates among gram-negative bacteria and its limited activity against gram-positive bacteria, such as streptococci, compared with newer alternatives. The dosing of these agents for patients with normal renal function using traditional dosing (ie, over 30 minutes) are:
    - Cefepime — 2 g IV every eight hours
    - Meropenem — 1 g IV every eight hours
    - Imipenem-cilastatin — 500 mg IV every six hours
    - Piperacillin-tazobactam — 4.5 g IV every six to eight hours; if there is significant concern for *Pseudomonas* infection (particularly in those who are severely ill or were not receiving fluoroquinolone prophylaxis at the time of onset of illness), 4.5 g IV every 6 hours should be given
    - Ceftazidime — 2 g IV every eight hours
- Other antibiotics (eg, aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen in patients with complicated presentations (eg, ***hypotension and/or mental status changes), focal findings (eg, pneumonia or cellulitis), or if antimicrobial resistance is suspected or proven.***
- Vancomycin (or other agents that target gram-positive cocci) is **not** recommended as a standard part of the initial regimen but should be added in certain patients, such as those with **suspected catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability.**
- The following antibiotics can be used when resistant infections are suspected
    - **MRSA** — Vancomycin, linezolid, or daptomycin; daptomycin should be avoided in patients with pneumonia because it does not achieve sufficiently high concentrations in the respiratory tract.
    - **VRE (vancomycin resistant enterococci)** — Linezolid or daptomycin
    - **ESBL (extended-spectrum beta-lactamases)**-producing gram-negative bacilli — A carbapenem (eg, imipenem, meropenem).
    - **Carbapenemase-producing bacteria**, including *Klebsiella pneumoniae* carbapenemase — Colistin or tigecycline.

4) Neutropenic enterocolitis (typhlitis)

- Neutropenic enterocolitis is a life-threatening, necrotizing enterocolitis occurring primarily in neutropenic patients. Other terms that have been used to describe this syndrome include "necrotizing enterocolitis" and "ileocecal syndrome."

- "Typhlitis" (from the Greek word "typhlon," or cecum) describes neutropenic enterocolitis of the ileocecal region; we prefer the more inclusive term "neutropenic enterocolitis," since other parts of the small and/or large intestine are often involved.
- The pathogenesis of neutropenic enterocolitis is incompletely understood. It probably involves a combination of factors, including mucosal injury by cytotoxic drugs or other means, profound neutropenia, and impaired host defense to invasion by microorganisms. The microbial infection leads to necrosis of various layers of the bowel wall. The cecum is usually affected, and the process often extends into the ascending colon and terminal ileum. The predilection for the cecum is possibly related to **its distensibility and its diminished vascularization relative to the rest of the colon.**
- Gross and histologic examinations may reveal **bowel wall thickening**, **discrete or confluent ulcers, mucosal loss, intramural edema, hemorrhage, and necrosis.**
- **MICROBIOLOGY** -various bacterial and/or fungal organisms, including gram-negative bacilli, gram-positive cocci, anaerobes (eg, *Clostridium septicum*), and *Candida* spp, are often seen infiltrating the bowel wall, and polymicrobial infection is frequent. Bacteremia or fungemia is also common; pathogens include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp, viridans group streptococci, enterococci, *Bacteroides* spp, *Clostridium* spp, and *Candida* spp

CLINICAL MANIFESTATIONS

- **Signs and symptoms** – Neutropenic enterocolitis must be considered in any severely neutropenic patient (absolute neutrophil count <500 cells/microL) who presents with ***fever and abdominal pain.*** The location of abdominal pain depends upon the location of the neutropenic colitis and is often in the ***right lower quadrant.*** Symptoms, including fever, frequently appear during the third week (**median 17 days**) after receiving cytotoxic chemotherapy, at a time when ***neutropenia is most profound.*** Additional symptoms may include abdominal distension, cramping, tenderness, nausea, vomiting, watery or bloody diarrhea, and frank hematochezia. Paralytic ileus may occur but is uncommon. Peritoneal signs and shock suggest the possibility of bowel wall perforation. Stomatitis and pharyngitis, suggesting the presence of widespread mucositis, may be present.
- Patients may remain febrile until recovery from neutropenia, independent of antimicrobial therapy. Patients developing neutropenic enterocolitis during chemotherapy are prone to develop this complication again during subsequent treatments.

DIAGNOSIS;

- Neutropenic enterocolitis is usually diagnosed by detection of the characteristic computed tomography (CT) findings in neutropenic patients presenting with fever and abdominal pain and tenderness. All patients suspected of having neutropenic colitis should undergo abdominal CT scanning.

- CT findings included bowel wall thickening (100 percent), mesenteric stranding (51 percent), bowel dilatation (38 percent), mucosal enhancement (28 percent), and pneumatosis (21 percent).
- ultrasound or plain radiographs of the abdomen(with 23 percent and 48 percent false negative respectively,which is 15% for CT)
- In addition to CT scanning, **blood and stool cultures** and ***C. difficile*** **toxin assays** should be performed.

TREATMENT

- Patients without complicated neutropenic enterocolitis (ie, perforation or severe bleeding) should receive nonsurgical management with ***broad-spectrum antimicrobials, bowel rest, nasogastric suction, intravenous fluids, nutritional support, and blood product support (packed red blood cells and fresh frozen plasma as needed).*** Although surgery is typically avoided in neutropenic and thrombocytopenic patients, surgical intervention is recommended for those with free perforation or another process that cannot be controlled medically (eg, ***persistent bleeding despite correction of coagulopathy and cytopenias***).
- The antimicrobial regimen should target likely pathogens as well as pathogens that have been detected from the patient's bloodstream. The regimen should include agents that are active against ***Pseudomonas aeruginosa, Escherichia coli, other enteric gram-negative bacilli, and anaerobes.***
- We suggest one of the following empiric regimens for patients with neutropenic enterocolitis provided that the patient does not have bacteremia with an organism that is resistant to the following agents:
- **Piperacillin-tazobactam**(for adults: 4.5 g IV every six hours; for infants <9 months: 80 mg/kg of piperacillin component IV every eight hours; for infants and children ≥9 months and ≤40 kg: 100 mg/kg of piperacillin component IV every eight hours; for children >40 kg: 3 g of piperacillin component IV every six hours or 4 g of piperacillin component IV every six to eight hours; the maximum daily dose of the piperacillin component is 16 g/day)
- **Cefepime plus metronidazole**(for adults: 2 g IV every eight hours; for children: 50 mg/kg IV every eight hours up to a maximum of 2 g per dose),metronidazole(for adults: 500 mg IV every eight hours; for children: 30 to 40 mg/kg IV per day in divided doses every six to eight hours, maximum daily dose 1500 mg/day).
- **Ceftazidime plus metronidazole** (for adults: 2 g IV every eight hours; for children: 50 mg/kg IV every eight hours up to a maximum of 2 g per dose)
- An antipseudomonal carbapenem (imipenem or meropenem) can also be used, but we reserve these agents for patients who are allergic to the other options or who are infected or colonized with an organism that is resistant to the other

recommended agents (eg, extended-spectrum beta-lactamase—producing Enterobacteriaceae).

- An antifungal agent should be started in neutropenic patients with protracted fever (>72 hours) despite broad-spectrum antibiotics. We favor an antifungal agent with activity against fluconazole-resistant *Candida* spp as well as *Aspergillus* spp.
- Examples of appropriate antifungal agents include an **echinocandin** for *Candida* species and **voriconazole or amphotericin B formulations** for both yeasts and molds.

PROGNOSIS

- Initial reports of patients with neutropenic enterocolitis described mortality rates between of **50 percent or higher.** Most deaths are attributed to transmural bowel necrosis, perforation, and sepsis. More recently, early recognition and progress in management have reduced mortality substantially, although no large series have been published.

Case reporting format for bedside, round, exam and case discussion

Dr. Mulualem. G,

- *This is a case report of CLD patient from my clinical year attachment bedside case at UOG Hospital.*

History

Identification

- This is Ato Meazaw wubie, a 56 years old, male, married, orthodox Christian, farmer, from Tach armachiho woreda, north Gondar zone, admitted to University of Gondar hospital, department of Internal medicine, Medical ward D, bed no #27 on Tikimt 24/2010 E.C.

Previous Admission

- None
- If there is previous admission which is unrelated to the current illness, you can document like these; E.g. 2003 E.C, TASH, Addis Ababa, HIV-associated cerebral toxoplasmosis, admitted for 03 months, treated with ART drugs and anti-toxoplasmosis drugs and discharged improved.

Chief compliant

- Abdominal distension of 03 months duration

HPI

This patient was last relatively healthy 03 months back, at which time he noticed Abdominal distension which initially started from RLQ, which gradually increase in size and progress to involve the whole abdomen and lower extremities within one month duration. Together with dragging sensation in the left upper abdomen, sense of fullness and early satiety.

04 months before the onset of abdominal distension, he experienced a stabbing RUQ abdominal pain which is moderate in severity and radiates to the back associated with low grade intermittent fever, coca colored urine and his families accidentally noticed yellowish discoloration of his eyes but no stool color change or itching sensation.

He has also unquantified but significant weight loss to the extent his trousers become loose, loss of appetite and easy fatigability.

For these, he visited a traditional healer where he was given unspecified herbal medication and cauterized at his arms, forearms, over the abdomen and back but he didn’t get any relief. Finally, he came to our hospital for better investigation and management.

- He drinks traditional areki half bottle 2 - 3 times per week for 5 years and then changed his drink to a beer of 10 to 15 bottles every Tuesday, Saturday and Sunday (average 37 bottles per week) for the past 8 years that means he drinks for a total of 13 years. which is estimated to be 70g alcohol intake daily for 13 years.
- No hx of blood transfusion, tattooing, contact with a jaundiced patient, IV drug abuse or MSP
- No hx of drug intake other than mentioned above
- No family hx of similar illness
- He usually eats injera made of “teff” and “machilla” and ‘’wott’’ made of “atter” and “dagusa” 3-4 times per day. Occasionally he eats meat during holidays
- He has coca colored discoloration of urine but no pain during urination, urgency, frequency or flank pain
- No hx of nasal bleeding, bloody vomiting or melena
- He has easy fatigability but no hx of tinnitus, blurring of vision or light headedness
- No hx of sleep disturbance, confusion, Forgetfulness, Abnormal body movement or LOC
- Has hx of river water contact but no hx of post river water contact itching
- No hx of dyspnea, orthopnea, PND or palpitation
- No hx of chronic cough, contact with chronic cougher or previous TB treatment
- No self/family hx of DM, HTN or asthma
- He was screened for RVI 2 months back and found to be NR.

Finally, he was admitted to our hospital supported physically by his families

Past illnesses

- No history of childhood illnesses like chicken pox, mumps or small pox. Not vaccinated.
- No history of previous surgery, trauma, psychiatry problems or drug allergy.

Review of system /ROS

- H.E.E.N.T
    - Head: No history of headache or head injury
    - Eyes: No history of blurring of vision, pain in the eyes, eye itching, or spontaneous lacrimation
    - Ears: No history of Earache, difficulty of hearing, ear discharge, vertigo or tinnitus
    - Nose: No history of nasal bleeding or discharge
    - Mouth and throat: No history of gum bleeding, tooth extraction

- LGS: No history of swelling in the neck, axilla or groin, No history of heat or cold intolerance.
- RS; No history of cough, chest pain or fast breathing
- CVS: Mentioned on HPI
- GIS; Mentioned on HPI
- GUS: Mentioned on HPI
- IGS: No history of skin rash or ulcers
- MSS: No history of loss of limb function, joint pain swelling over the extremities or deformity.
- CNS: No hx of weakness of extremities. See HPI

Personal History

- He was born and raised in Tach armachiho in 1954 E.C, where he lived all his life. He had a healthy childhood and was an active boy who liked helping his father around the farm. He didn't attend formal education but he is able to read and write.
- He is a farmer and also raises cattle, sheep and goat. He claims his income is enough to support the family.
- He has 4 boys and one daughter. All are alive and healthy.

Family History

- Both his father and mother are dead. His father died while he was child at unknown age by unknown cause while his mother died 5 years ago at age 69 by natural cause.
- He has two sisters and one brother. All are alive & well.
- No family history of DM, hypertension, Asthma, tuberculosis, allergy or sudden deaths.

Physical examination

General Appearance

- conscious & cooperative, **chronically sick looking**, not in cardiopulmonary stress, looks well nourished

Vital signs

- BP: 110/70mmHg, right arm, sitting position → normotensive
- PR:95 beat per minute/bpm, at right radial artery, regular & full volume → normal
- RR: 18 breath/min, shallow & regular → normal
- T^0: 36.2^{0}c, at axillary, at 8:00 DLT
- MUAC: 24 cm
- BMI: not done (since he has ascites)

H.E.E.N.T

- Head: Normal male type hair distribution, No visible scar over the scalp or tenderness
- Ears: Normal contour of pinna, Clear external ear canal, No mastoid or tragus tenderness
- Eyes: **Icteric sclera**, Pink conjunctivae, No periorbital edema
- Nose: central nasal septum. There is no polyp or active discharge
- Mouse and throat: No fissure or ulceration on the lip, the gums are intact, no active bleeding. There are no carious teeth, extraction, dentures or filling. no atrophied papillae of tongue, the buccal mucosa is pink & wet.

Lymphoglandular system (LGS)

- There is no significantly enlarged lymphadenopathy in peripherally accessible lymph node areas
- The thyroid gland is not enlarged
- There is no breast lump (gynecomastia)
- No parotid gland enlargement
- No testicular atrophy

Respiratory System (RS)

- Inspection
    - There is **grade II clubbing of fingers**, but no central or peripheral cyanosis
    - Symmetric chest wall that moves with respiration
    - No chest wall deformity
    - No subcostal or intercostal retraction
    - No use of accessory muscles of respiration\
    - Shallow and regular breathing pattern
- Palpation
    - There is no chest wall tenderness or subcutaneous emphysema
    - Centrally located trachea
    - Comparable tactile fremitus bilaterally
    - Symmetrically normal chest expansion bilaterally which slides 5cm by measuring tape method.
- Percussion
    - Resonant percussion note all over the lung field
    - There is no dullness
    - diaphragmatic excursion = 5cm bilaterally
- Auscultation
    - Vesicular breath sound all over the lung field
    - No added respiratory sound
    - Comparably normal air entry bilaterally

Cardiovascular system (CVS)

- Arterial examination

  - All accessible peripheral arteries are palpable, full in volume and regular in rhythm
- Venous examination
  - No distended neck veins
  - JVP = 3cm
- Precordial Examination
  - Inspection
    - Active precordium
    - AI @5th ICS medial to left MCL
    - No precordial buldge or scar
  - Palpation
    - Palpable heart sounds
    - PMI @5th ICS medial to left MCL which is Localized, tapping and non-sustained
    - No heave or thrill
  - Auscultation
    - S1 & S2 are well heard
    - No murmur or gallop

Abdominal examination

- Inspection
  - **Grossly / Symmetrically distended abdomen**
  - **Flanks are full**
  - **Everted umbilicus with circular slit**
  - **superficially distended and tortuous abdominal vessels which drain away from umbilicus during palpation**
  - No visible scar, straie, pigmentation or peristalsis
  - Hernia sites are free
- Auscultation
  - Normoactive bowel sounds (18 kicks/min)
  - No bruit over abdominal aorta, renal arteries, iliac arteries, liver or spleen
- Palpation
  - Superficial palpation
    - No superficial tenderness
    - No superficially palpable mass
  - Deep palpation
    - **Enlarged/ ballotable mass over the LUQ which is 13 cm from left costal margin along the splenic growth line, non-tender, firm in consistency, smooth surface, sharp edge, Palpable medial notch, doesn't allow finger to pass below left costal margin, Moves with respiration, Not bimanually palpable**
    - No direct/rebound tenderness, guarding or rigidity
    - Liver is not palpable
    - kidney is not bimanually palpable bilaterally.
- Percussion
  - Tympanic percussion note except the flanks (i.e. **dullness over the flanks)**

  - There is **shifting dullness of 2cm** but no fluid thrill
  - TVLS = 10cm along MCL

Genitourinary System (GUS)

- No costo-vertebral angle tenderness (CVAT)

Integumentary System (IS)

- No spider angioma or spider nevi
- No palmar erythema, palmar or plantar pallor
- No skin or nail pigmentation
- No bruising or purpura
- No axillary or pubic hair loss
- No scratch marks

N.B. these finding are pertinent negative for CLD, in other cases you can report like these;

- No palmar or plantar pallor
- No rash, scar or ulcer

Musculoskeletal System

- Look; there is leg swelling but no deformity
- Feel; There is **grade II pedal and pretibial pitting edema**, no tenderness
- Move; intact active and passive range of movement in all extremities
- Measure; comparable circumference and length of extremities

Nervous system

- Level of consciousness
  - GCS = 15/15 (E4V5M6), conscious and alert
- CN examination
  - CN-I: He can smell soap via each nostril.
  - CN-II:
    - He can differentiate 2 fingers at about 6 meters. (Visual Acuity)
    - He sees waggling of finger approximately 100^0 from axis of eye. (Visual Fields)
    - He differentiates green and red colours. (Colour Appreciation)
    - Normal direct and consensual pupillary light reflex
  - CN-III, IV & VI:
    - The eyes can move in all directions. There is no nystagmus or diplopia. The pupils are round, regular in outline and equal in size. They react to light directly and consensually.
  - CN-V:

  - He identifies light touch and pin prick over the mandibular, maxillary and ophthalmic areas of the face.
  - He closes his eyes at the touch of the cornea with a cotton swab.
  - Contraction of the temporal and masseter muscles is symmetrical and strong while clenching his teeth.
- CN-VII:
  - The face is symmetrical at rest and during voluntary movements (smiling, frowning).
  - He can smile, frown his forehead, puff out his cheeks
  - can close both eyes equally and forcefully against resistance.
  - Intact nasolabial fold
  - Intact corneal reflex
- CN-VIII:
  - He can hear rubbing of the fingers on both ears.
- CN-IX & X:
  - The soft palate rises in the midline when saying ‘ah!
  - Centrally located uvula
  - He can swallow his saliva
- CN-XI:
  - The Sternocleidomastoid and trapezius muscles contract on turning the head and on shrugging the shoulder against resistance, respectively
- CN-XII:
  - The tongue protrudes in the midline and shows no fasciculation or atrophy.

- Motor examination
  - Inspection
    - The limbs are centrally positioned, no inward or outward rotation
    - Comparable muscle bulk between the left and the right side of both upper and lower extremities.
    - There is no spontaneous as well as induced fasciculation.
  - Palpation
    - Tone and power

	TONE		POWER	
	Upper	Lower	Upper	Lower
Right	Normo-tonic	Normo-tonic	5/5	5/5
Left	Normo-tonic	Normo-tonic	5/5	5/5

    - Reflexes
      - Superficial
        - ✓ Abdominal reflex is present both in upper and lower quadrants.
        - ✓ Corneal reflex is intact in both eyes.
        - ✓ Plantar reflex is down going on both sides.

- DTR

	Biceps	Triceps	Brachioradialis	Patellar	Ankle
Right	++	++	++	++	++
Left	++	++	++	++	++

- Sensory examination
  - Primary sensory exam
    - He identifies light touch and pin prick over the extremities and trunk.
    - He is able to recognize different movements of the toes with his eyes closed. (Position sense)
    - Vibration sense was not assessed due to lack of Tuning Fork.
  - Cortical sensory exam
    - He appreciates the form of a key by means of only touch (Stereognosis)
    - He recognizes writings of different numbers on his palm (Graphesthesia)
    - He is able to differentiate 2 pin pricks up to 4 mm apart over the finger tips (2 pt discrimination).
- Coordination
  - Finger to nose, heal to shin and rapid alternating movement of the arm were done without any abnormalities.
- Meningeal irritation signs
  - No neck stiffness.
  - Kernig's Sign is negative.
  - Brudzinski's Sign is negative

Subjective summary

- A 56 years old male patient presented with abdominal distension of 3 months duration associated with dragging sensation in the left upper abdomen, sense of fullness and early satiety.
- 04 months before the onset of abdominal distension, he experienced a stabbing RUQ abdominal pain, low grade intermittent fever, coca colored urine and yellowish discoloration of the eyes.
- He has also unquantified but significant weight loss, loss of appetite and easy fatigability.
- He has history of herbal medication intake and chronic alcohol intake for the past 13th years.

Objective summary

- conscious & cooperative, chronically sick looking, not in cardiopulmonary stress, looks well nourished
- BP: 110/70mmHg

- PR: 95 bpm
- RR: 18 breath/min
- T^0: 36.2^0c
- He has
  - Icteric sclera
  - grade II clubbing of fingers
  - Grossly distended abdomen
  - Flank fullness
  - Everted umbilicus with circular slit
  - superficially distended and tortuous abdominal vessels which drain away from umbilicus during palpation
  - shifting dullness of 2cm
  - flank dullness
  - Ballotable mass over the LUQ which is 13 cm from left costal margin along the splenic growth line, non-tender, firm in consistency, smooth surface, sharp edge, Palpable medial notch, doesn't allow finger to pass below left costal margin, Moves with respiration, Not bimanually palpable → marked splenomegaly
  - grade II pedal and pretibial pitting edema

Investigations done

Investigation	Result	Interpretation
CBC	WBC = 6.6 x 10^3 Neut = 85.8 % Lymph = 9.9 % HGB = 9.1 mg/dl HCT = 27.1 mg/dl PLT = 111 x 10^3 MCV = 88.3 MCH = 29.6 MCHC = 33.6	Moderate anaemia Thrombocytopenia
U/A	WBC = 2/HPF PH = 6.0 SPG = 1.010 Protein = +1 Others = neg	Non revealing
Liver enzymes	SGOT = 58 (1.4 X UNL*) SGPT = 30	Normal
LFT	Albumin = 3.6 g/dl Total protein = 5.1 g/dl	Low
Ascetic fluid analysis	Cell count = 150/mm^3, Neut = 80%, Lymph = 10.1% Glucose = 53 mg/dl Protein = 8mg/dl AFB = neg Gram stain = neg Culture = no organism identified	Normal
PM	NcNc	

Serum electrolytes	NA$^+$ = 142.8 K$^+$ = 3.53 Cl$^-$ = 103	Normal
PICT	NR	
RBS	156mg/dl	Normal
RFT	Creatinine = 0.54 Urea = 12	Normal
* UNL = Upper normal limit		

Recommended Investigations to be done

A) HBsAg
B) Direct and total bilirubin
C) Abdominal U/S
D) Echo

DDX from most likely to list likely

i. Chronic liver disease (CLD)
ii. Right sided heart failure
iii. Chronic constrictive pericarditis
iv. Nephrotic syndrome

Discussion on differentials from least likely to most likely

Nephrotic syndrome (NS)

Definition;
Etiology;
Pathophysiology;
Epidemiology;
Clinical features;

write from the corresponding topics of nitsbin above, Harrison and uptodate (this is for other DDX also)

Conclusion;
This patient has ascites with grade II pedal and pretibial edema, easy fatigability and loss of appetite which support nephrotic syndrome. But stabbing RUQ abdominal pain jaundice and the pattern of edema can't be explained by NS. For the diagnosis of NS, Nephrotic range proteinuria and Serum albumin concentration < 3 g/dL are used. But this patient has only protein +1 and serum albumin of 3.6g/dl which doesn't support NS. Epidemiologically, unlike children, NS is not common in adults. So, nephrotic syndrome as a diagnosis is unlikely for this case.

Chronic constrictive pericarditis

Conclusion;

This patient has ascites with grade II pedal and pretibial edema, easy fatigability and weight loss which goes with constrictive pericarditis. The absence of retrosternal chest pain, elevated JVP, tender hepatomegaly and pericardial friction rub goes against constrictive pericarditis. In developing world infectious (especially TB) is the most common cause of constrictive pericarditis. This patient has no hx of contact or TB infection and from ascitic fluid analysis AFB is negative which may help us to r/o constrictive pericarditis. So, constrictive pericarditis as a diagnosis is less likely for this case.

Right sided heart failure (RSHF)

Conclusion;

This patient has ascites with grade II pedal and pretibial edema, easy fatigability, weight loss and splenomegaly which goes with RSHF. The absence of elevated JVP, tender hepatomegaly goes against RSHF. RSHF is usually from left sided heart failure (LSHF) and Isolated RSHF is cor pulmonale. This patient has no hx of LSHF or cor pulmonale which may help us to r/o RSHF. So, right sided heart failure as a diagnosis is less likely for this case. But I strongly recommend Echocardiography for this patient.

Chronic liver disease (CLD)

Conclusion;

This patient has Ascites, leg edema and splenomegaly which can be explained by Portal Hypertension secondary to decompensated CLD.

04 months before the onset of abdominal distension, he also experienced a stabbing RUQ abdominal pain, low grade intermittent fever, coca colored urine and yellowish discoloration of the eyes, which suggest there was hepatitis which end up with cirrhosis.

He has history of chronic alcohol intake for the past 13th years which strongly suggest alcoholic liver disease.

Grade II clubbing, icteric sclera can be explained by peripheral stigmata of CLD. Investigation wise the presence of anemia, thrombocytopenia and hypoalbuminemia suggest lifer synesthetic dysfunction. So, CLD is the most likely diagnosis for this case

Final assessment

Decompensated CLD (evidenced by ascites + Splenomegaly 2ry to portal HTN) secondary to Alcoholic Liver disease r/o Chronic viral hepatitis

References

- Harrison's principle of internal medicine 20th edition

- UpToDate, © 2018, version 2.0

Part II

Short cases

Chapter 1; Physical examination

Dr. Mulualem. G

Tips for short exams

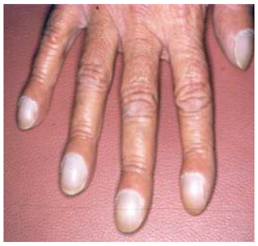
- ☛ You are going to be asked by your senior to do one system examination (e.g do posterior chest exam, do precordial examination, show me lower motor examination)
- ☛ During exams you are evaluated not only with your scientific background but also with, your confidence, skill of examination and ability to pick up findings, patient approach (like introducing yourself and greeting)
- ☛ After completing the examination, you are expected to
    - ✓ Conclude your physical findings (for example; after doing from inspection to auscultation of posterior chest examination, your conclusion may be pleural effusion)
    - ✓ List down possible DDX of your findings from cmn to less cmn in order
    - ✓ Investigation for your Top DDX
    - ✓ Mgt principle for your Top DDX

1.1 Respiratory System

- You may be asked the following in RS examination
    - ☛ Do posterior chest examination → most cmnly asked
    - ☛ Do anterior chest examination
    - ☛ Do respiratory system examination

1.1.1 Physical examination findings

N.B normal RR = 8 - 22 BPM

<table>
<tr><th colspan="2">Examination techniques</th><th>Possible abnormal findings and their causes</th></tr>
<tr><td>Inspection (5 S)</td><td>❖ Cyanosis and clubbing
❖ Symmetry
❖ Shape (chest wall deformity)
❖ Subcostal or intercostal retraction, use of accessory muscles of respiration
❖ Breathing pattern
✓ Shallow and regular or not</td><td>☛ Clubbing
✓ Grading
1. Sponginess or softening of nail fold
2. Obliteration of hyponychial angle (nail fold ≥ 180^0)
3. Curvature (convexity) → like bird's peak
4. Biconvexity (drum steak appearance)
5. Associated arthropathy

✓ Causes of clubbing
<table>
<tr><th>Respiratory system→ ABCDE</th><th>CVS</th><th>GIT → 4C's</th></tr>
<tr><td>A. Lung Abscess
B. Bronchiectasis
C. Cancer (Bronchogenic ca, mesothelial ca or metastasis to lung)
D. Desaturation (hypoxia)
E. Empyema → TB
F. Fibrosing alveolitis (cystic fibrosis)</td><td>1. IE
2. Cyanotic CHD (PDA, TOF)</td><td>1. Cirrhosis
2. Cancer (GI lymphoma)
3. IBD (CD)
4. Coeliac disease</td></tr>
</table>
☛ Respiratory distress signs
✓ Tachypnoea
✓ Flaring of the alanasae
✓ Use of accessory muscles of respiration
❖ Sternomastoid muscle
❖ Strap muscles (sternothyroid, sternohyoid, thyrohyoid)
❖ platysma
✓ Sub clavicular, subcostal or intercostal retraction
☛ Chest lag/delay
✓ Ipsilateral
✚ Pleural effusion
✚ Pneumothorax
✚ Consolidation
✚ Atelectasis
✚ fibrosis
✓ bilateral
✚ Emphysema
✚ ILD
✚ Bilateral fibrotic lung
☛ Abnormal breathing patterns → causing examples
✓ Tachypnia → severe pneumonia, decreased CO
✓ Bradypnea → barbiturate poisoning
✓ Paradoxical breathing → diaphragmatic paralysis
✓ Kussmauls breathing (deep, labored, fast breathing followed by apnoea) → Metabolic acidosis (DKA, ureamic encephalopathy, hepatic encephalopathy)
✓ Chyne stokes breathing → CHF, stroke
✓ Apneustic breathing → pontine damage
✓ Ataxic breathing → medullary compression (trans tentorial herniation)
☛ Chest wall deformities → causing examples</td></tr>
</table>

<table>
<tr><td></td><td></td><td>✓ Barrel chest → COPD (emphysema), Chronic asthma, aging
✓ Pectus excavatum (funnel chest)
✓ Pectus carinatum (pigeon chest)
✓ Kyphosis
✓ Scoliosis
✓ Kyphoscoliosis →idiopathic, rickets, severe childhood asthma</td></tr>
<tr><td></td><td colspan="2">**Reporting format for normal chest inspection finding**
☛ There is no central or peripheral cyanosis or clubbing, symmetric chest wall that moves with respiration, no chest wall deformity, no subcostal or intercostal retraction, no use of accessory muscles of respiration, shallow and regular breathing pattern</td></tr>
<tr><td rowspan="2">Palpation (4T)</td><td>✚ Tenderness and subcutaneous emphysema
✚ Tracheal location and tracheal tug (normally trachea slightly deviate to the right side)
✚ Tactile fremitus
✚ Chest expansion (normal = 4 -6cm)
  ✓ Tape method
  ✓ Hand grip method</td><td>❖ Chest wall tenderness → rib fracture
❖ Subcutaneous emphysema → pneumothorax
❖ Tracheal deviation
<table>
<tr><th>Away from the lesion</th><th>Towards the lesion</th></tr>
<tr><td>➢ Massive pleural effusion
➢ Pneumothorax
➢ Mediastinal mass
N.B 4T’s of mediastinal mass
✚ Terrible lymphoma (NHL is cmn)
✚ Thyroid mass (retrosternal extension of thyroid mass)
✚ Teratoma
✚ Thymoma
➢ COPD</td><td>➢ Upper lobe fibrosis
➢ Atelectasis
➢ Pneumonectomy</td></tr>
</table>
❖ Tracheal tug → COPD
❖ Increased tactile fremitus → consolidation
❖ Decreased chest expansion
<table>
<tr><th>Ipsilaterally (over the affected side of lung)</th><th>Bilaterally</th></tr>
<tr><td>✚ Pleural effusion
✚ Pneumothorax
✚ Consolidation
✚ Atelectasis
✚ fibrosis</td><td>✚ Emphysema
✚ ILD
✚ Bilateral fibrotic lung</td></tr>
</table>
</td></tr>
<tr><td colspan="2">**Reporting format for normal chest palpation finding**
☛ There is no chest wall tenderness or subcutaneous emphysema, centrally located trachea, comparable tactile fremitus bilaterally, symmetrically normal chest expansion bilaterally which slides 5cm by measuring tape method.</td></tr>
</table>

<table>
<tr>
<td rowspan="2">Percussion</td>
<td>➢ Percussion note

Normal = resonant
➢ Diaphragmatic excurtion
✓ normal = 5 - 6 cm
N.B. you can't do diaphragmatic excursion in
☛ if there is dullness
☛ tender chest wall
☛ respiratory distress and patient with O_2
☛ if patient is not cooperative (e.g. coma)</td>
<td>➢ Dullness to percussion
✓ Relative dullness → consolidation
✓ Stony (absolute) dullness → pleural effusion, hemothorax, empyema
➢ Hyper resonant percussion note → emphysema, pneumothorax
➢ Diaphragmatic excursion decreases ipsilaterally in
✓ Pleural effusion
✓ Pneumothorax
✓ Fibrosis
✓ Atelectasis</td>
</tr>
<tr>
<td colspan="2">Reporting format for normal chest percussion finding
☛ Resonant percussion note all over the lung field, there is no dullness, diaphragmatic excursion = 5cm bilaterally</td>
</tr>
<tr>
<td rowspan="2">Auscultation</td>
<td>☛ Breath sound
✓ Vesicular → normal
✓ Broncho vesicular
✓ Bronchial
✓ Tracheal
☛ Added respiratory sounds
☛ Air entry</td>
<td>➢ Bronchial breath sound
✓ Consolidation
✓ On top of pleural effusion
✓ Fibrosis
➢ Added respiratory sounds
✓ Crackles
<table>
<tr><th>Fine crackles (rales)</th><th>coarse crackles (crepitation)</th></tr>
<tr><td>✚ Pulmonary edema <i>(bilateral basal rales)</i>
✚ Fibrosing akveolitis</td><td>✚ Consolidation
✚ TB
✚ COPD
✚ Bronchiectasis</td></tr>
</table>
✓ Wheeze →Bronchial asthma, COPD, bronchiectasis, foreign body obstruction <i>(unilateral wheeze),</i> hilar LAP of TB, cardiac asthma <i>(pulmonary edema from CHF→ have basal rales with wheeze),</i> tracheal fibrosis
✓ Rhonchi → usually over the bronchi (i.e. large airways), COPD
✓ Pleural friction rub → pleurisy from TB/ pneumonia, pulmonary infarction
✓ Transmitted voice sounds (vocal resonance) → heard clearly in consolidation
✚ Aegophony
✚ Bronchophony
✚ Whispering pectoriloeqy
➢ Airy entry
✓ Decreased/ absent → pleural effusion, pneumothorax, atelectasis, pleural thickening
✓ Increased → consolidation
✓ Decreased → COPD</td>
</tr>
<tr>
<td colspan="2">Reporting format for normal chest auscultation finding
☛ Vesicular breath sound all over the lung field, no added respiratory sound, comparably normal air entry bilaterally</td>
</tr>
</table>

1.1.2 pleural effusion

Findings	**DDX**		**IX**	**Mgt principle**
	Transudative	**Exudative**		
✓ Trachea deviated away from a massive effusion ✓ Decreased tactile fremitus ✓ Ipsilateral chest lag (reduced chest expansion) ✓ Stony dullness ✓ Absent air entry ✓ BBS Above the effusion (not always) ✓ Pleural friction rub	1. CHF 2. Constrictive pericarditis 3. Nephrotic syndrome 4. CLD (cirrhosis) 5. Hypothyroidism 6. Meig's syndrome	1) Pneumonia with Parapneumonic effusion 2) Disseminated TB to lung and pleura 3) Lymphoma (primary effusive lymphoma) 4) lung cancer (bronchogenic, mesothelioma or metastasis to lung) 5) Pulmonary infarction 6) Connective tissue diseases (SLE) 7) Traumatic effusion 8) Acute pancreatitis	1. **Pleural fluid analysis** → *refer nitsibin under pleural tap* 2. **CBC** 3. **CXR** ✓ May not be visible if the amount is <250 ml ✓ Blunted/ obliterated costophrenic angle ✓ Radio-opaque density extending from the base ✓ Meniscus sign at upper surface ✓ Mediastinal shift away from the effusion → if huge effusion 4. **Chest U/S** ✓ Identify loculated effusion ✓ differentiate fluid from fibrosis ✓ identification of thoracentesis site 5. **Chest CT** ✓ Aids in differentiation of ❖ Consolidation vs effusion ❖ Cystic vs solid lesions ❖ Peripheral lung abscess vs loculated empyema ✓ Aids in identification of ❖ Necrotic areas ❖ Pleural thickening, nodules, masses ❖ Extent of tumour 6. **Pleural Biopsy → diagnostic for pleural TB** 7. **U/A →** for NS screening 8. **Serum albumin level** 9. **LFT →** if you suspect CLD 10. **ECG and Echo** → if you suspect CHF 11. **TFT** → if you suspect hypothyroidism	✓ Put on intranasal O_2 if saturation is < 90% ✓ Therapeutic tap for huge effusion ✓ Chest decompression ▪ Chest tube insertion ▪ Large bore needle insertion ✓ Antibiotics ✓ Management of the underlying cause

Reporting format of pleural effusion

- ❖ **Inspection**
- ❖ **Palpation**

  Centrally located trachea, tactile fremitus decreased over the posterior lower 1/3rd of right/left chest, decreased chest expansion over the right side by hand grip method
- ❖ **Percussion**

  Stony dullness over the posterior lower 1/3rd of right/left chest
- ❖ **Auscultation**

Absent air entry over the posterior lower 1/3rd of right/left chest

1.1.3 Consolidation

Findings	DDX	IX	Mgt principle
✚ Ipsilateral chest lag ✚ Increased tactile fremitus ✚ Relative dullness ✚ Auscultation findings ❖ Course crepitation ❖ BBS ❖ Pleural friction rub ❖ Vocal resonance ▪ Aegophony ▪ Bronchophony ▪ Whispering pectoriloquy	✚ Pneumonia ✚ TB → apical consolidation ✚ Above pleural effusion ✚ pulmonary haemorrhage ✚ ARDS ✚ Pulmonary edema ✚ Aspiration ✚ Lung abscess ✚ Bronchiectasis ✚ Neoplasm (Bronchogenic ca) ✚ Pulmonary infarction	✚ **CXR** ✓ Consolidation → silhouetting sign, *Air bronchograms* ✓ Parapneumonic effusion ✓ Lung abscess ✚ **ESR** → elevated especially in TB and pneumonia ✚ **CBC** ✓ leucocytosis ✚ **IX based on the suspected case** → e.g TB work up	✓ Put on intranasal O_2 if saturation is < 90% ✓ Antibiotics ✓ Management of the underlying cause

Reporting format of consolidation

❖ **Inspection**

❖ **Palpation**

Centrally located trachea, tactile fremitus increased over the posterior lower 1/3rd of right/left chest, decreased chest expansion over the right/left side by hand grip method

❖ **Percussion**

relative dullness over the posterior lower 1/3rd of right/left chest

❖ **Auscultation**

Coarse crepitation (± BBS → *it needs experienced examination*) over the posterior lower 1/3rd of right/left chest

1.1.4 Pulmonary edema

Findings	DDX	IX	Mgt principle
✚ Tachypnea ✚ Cardiorespiratory distress ✚ Desaturation ✚ High/normal BP ✚ Bilateral basal rales ✚ Relative dullness ✚ Decreased air entry ✚ Wheeze ✚ Raised JVP ✚ S3 gallop	✚ Cardiogenic ✓ CHF ✓ Hypertensive emergencies ✓ ACS ✓ Arrythmia like AF ✚ Non cardiogenic ✓ **ARDS** ✓ **high altitude** ✓ **neurogenic pulmonary edema** ✓ DKA ✓ Pulmonary embolism ✓ Eclampsia ✓ Transfusion-related acute lung injury (TRALI). ✓ Opioid overdose	✚ CXR ✓ bat wing appearance ✓ cephalization (Diversion of Blood vessel circulation towards the Apex) ✓ Kerl B lines ✚ IX for the underlying cause ✓ RBS → DKA ✓ ECG & ECHO → CHF ✚ Other CHF work up	✚ O_2 ✚ Strong analgesics like morphine ✚ Lasix ✚ If no response to diuretics use vasodilators like Nitroglycerine. N.B. ✚ Early oxygenation and ventilation support is life saving ✚ Treatable precipitating causes (eg. Arrhythmia, hypertensive crisis, ACS) *For more refer Pulmonary edema under CHF from long case of nitsbin (click here → [1.10.2 Pulmonary edema](#))*

Reporting format of pulmonary edema

❖ **Inspection**
There is subcostal and intercostal retraction, use of accessory muscles and flaring of alanasae

❖ **Palpation**
CVS→ bilaterally distended neck veins, JVP is 5cm above the heart level (raised),

❖ **Percussion**
relative dullness over the posterior lower 1/3rd of chest bilaterally

❖ **Auscultation**
Bilateral basal rales over the posterior lower 1/3rd of chest
Decreased air entry over the posterior lower 1/3rd of chest bilaterally

CVS → there is S3 gallop.

1.1.5 Pneumothorax

Findings	DDX		IX	Mgt principle
	Spontaneous	Traumatic		
✓ Trachea deviated away from pneumothorax ✓ Decreased tactile fremitus ✓ Ipsilateral chest lag (reduced chest expansion) ✓ Subcutaneous emphysema ✓ Decreased tactile fremitus ✓ Hyper resonant to percussion ✓ Absent air entry ✚ If there is tension pneumothorax ▪ Cyanosis ▪ Tachypnoea ▪ Hypotension	1. Emphysema →with rupture of bullae 2. Pulmonary TB 3. Rarely Bronchial asthma and lung abscess	1) penetrating chest injury 2) rib fracture 3) Iatrogenic ✓ During Pleural or pericardial aspiration ✓ During central venous catheterization	**1. CXR** ✚ Hypo dense (extremely dark) on the affected side ✚ Mediastinum shift to opposite side ✚ Tracheal shift to opposite side ✚ Visceral pleural edge is visible ✚ Absent broncho vascular markings peripherally ✚ Loss of lung volume on the affected side 2. Pulmonary function test 3. Other Baseline IX 4. IX based on the underlying cause	✓ Put on intranasal O_2 if saturation is < 90% ✓ Immediate chest decompression ▪ Chest tube insertion ▪ Large bore needle insertion ✓ Management of the underlying cause

Reporting format of pneumothorax

- ❖ **Inspection**
- ❖ **Palpation**
  Trachea deviated to the opposite side, tactile fremitus decreased over the posterior right/left chest, decreased chest expansion over the right/left side by hand grip method
- ❖ **Percussion**
  Hyper resonant to percussion over the posterior right/left chest
- ❖ **Auscultation**
  Absent air entry over the posterior right/left chest

1.1.6 Pulmonary fibrosis

Findings	DDX		IX	Mgt principle
	Upper lobe; S2CHA2RT	**Lower lobe**; RASCO		
- Cyanosis - Clubbing - Trachea shifts towards the lesion in upper lobe fibrosis - Decreased chest expansion ipsilaterally - Fine crackles	- Silicosis - Sarcoidosis - Coal-worker's pneumoconiosis - Histoplasmosis - Ankylosing spondylitis - Allergic broncho-pulmonary aspergillosis - Radiation - Tuberculosis	- Rheumatoid arthritis (RA) - Asbestosis - Scleroderma - Cryptogenic fibrosing alveolitis - Others: drugs- ✓ busulphan, ✓ bleomycin, ✓ methotrexate, ✓ hydralazine, ✓ amiodarone	✓ *Refer long case of nitsibin → IX of ILD*	- *Refer long case of nitsibin → mgt of ILD*

Reporting format of pulmonary fibrosis

- **Inspection**
  There is central and peripheral cyanosis, there is grade II clubbing of fingers
- **Palpation**
  Trachea deviated to the same side of lesion (*please say right or left based on your finding),* decreased chest expansion over the right/left side by hand grip method
- **Percussion**
- **Auscultation**
  Fine crackles over the posterior right/left chest

1.1.7 lung collapse (Atelectasis)

Findings	DDX	IX	Mgt principle
- Trachea - deviates towards the collapsed lung ▪ Due to compensatory hyperinflation on the opposite lung - Reduced chest expansion ipsilaterally - Relative dullness over the collapsed lung - Decreased/ absent air entry with/without BBS above the collapse	- **Obstruction (resorption)** ✓ Mucous obstruction → cmn cause ▪ Bronchial asthma ▪ Bronchiectasis ▪ COPD (chronic bronchitis) ▪ Post-operative obstruction ✓ Tumours or mass ▪ Bronchogenic ca ▪ Hilar LAP of TB - **Compression** ✓ Pleural effusion ✓ Pneumothorax ✓ Elevated diaphragm in bed ridden pt - **Contraction** ✓ Fibrosis of lung or pleura	- CXR ✓ ***Direct signs*** ▪ Displacement of interlobular fissure ▪ Loss of aeration of the lung ▪ Vascular and bronchial overcrowding ✓ ***Indirect signs*** ▪ Elevation of the hemidiaphragm ▪ Mediastinal displacement ▪ Hilar displacement ▪ Compensatory hyperinflation	✓ Put on intranasal O_2 if saturation is < 90% - Management of the underlying cause

	N.B. From the three mechanisms of lung collapse, all are reversible except contraction	✚ CT scan ✚ Other Baseline IX ✚ IX based on the underlying cause	

Reporting format of atelectasis

- **Inspection**
- **Palpation**
  Trachea deviated to the same side of lesion (*please say right or left based on your finding),* decreased chest expansion over the right/left side by hand grip method
- **Percussion**
  There is relative dullness over the posterior right/left chest
- **Auscultation**
  Absent air entry over the posterior right/left chest

1.1.8 emphysema

Findings	DDX	IX	Mgt principle
✚ Respiratory distress (use of accessory muscle of Respiration, Subcostal or intercostal muscle retraction, tripod positioning) ✚ Pink puffers, tilt forward → no more used ✚ Pursing of lips → close lips tightly during ✚ Barrel shaped chest → AP diameter of chest > lateral diameter due to hyperinflation ✚ Hoover's sign +ve → paradoxical inward movement of ribcage with respiration ✚ Decreased chest expansion bilaterally ✚ hyper resonant percussion note ✚ loss of cardiac and liver dullness → flattening of diaphragm ✚ poor diaphragmatic excursion → enlarged liver volume ✚ decreased Air entry bilaterally ✚ coarse crepitation (crackles) and wheeze at lung bases throughout the respiratory cycle	✚ Chronic bronchitis ✚ Pneumothorax ✚ Bronchiectasis ✚ Post TB fibrosis ✚ Refractory Asthma ✚ Chest wall deformity ✚ ILD(IPF) ✚ CHF ✚ Lung ca ✚ Chronic PTE ✚ Neuromuscular disorders ✚ CF	✓ *Refer long case of nitsibin → IX of COPD*	✚ *Refer long case of nitsibin → mgt of COPD*

Reporting format of emphysema

- **Inspection**
  There is use of accessory muscle of Respiration, Subcostal or intercostal muscle retraction
- **Palpation**
  Centrally located Trachea, decreased chest expansion bilaterally by hand grip method
- **Percussion**
  Hyper resonant to percussion over the posterior right/left chest
- **Auscultation**
  Decreased air entry over the posterior chest bilaterally, coarse crepitation over the posterior chest bilaterally

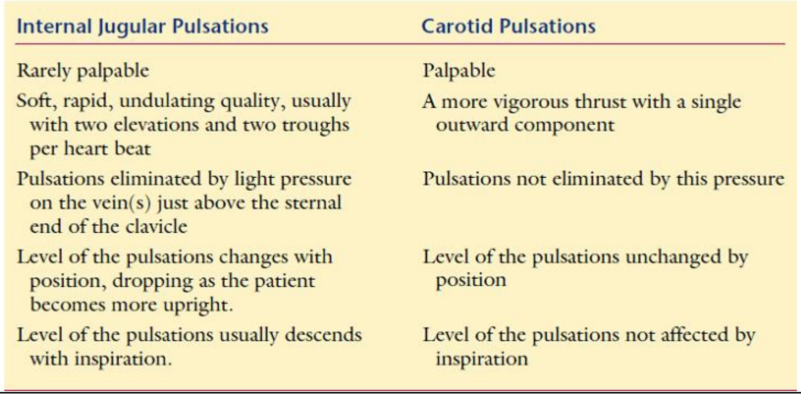
1.2 Cardiovascular System

- You may be asked the following in CVS examination
  - ☛ Do precordial examination → most cmnly asked
  - ☛ Check for congestion (assess signs of CHF)
  - ☛ Do CVS examination

1.2.1 Physical examination findings

N.B **normal PR = 60 – 100 BPM**

Examination techniques		Possible abnormal findings and their causes
General apperance		✓ Cardio pulmonary distress ▪ Distended neck vein ▪ Raised JVP ▪ Diaphoresis and cyanosis ▪ Hyperactive precordium ✓ Cyanosis ✓ Pallor ✓ Clubbing
Arterial examination	BP	✓ OHT→ anaemia, autonomic neuropathy (DM, ureamia, RVI), Drugs (vasodilators, diuretics, anti-depressants), endocrine (Addison's disease, hypopituitarism), idiopathic ✓ **Wide pulse pressure** (difference b/n SBP and DBP 30-60 normally. If > 60 it is Wide pulse pressure and if <30 it is narrow pulse pressure) → **AR, Anaemia, thyrotoxicosis, AV malformation, Beriberi, pregnancy** ✓ **Narrow pulse pressure** → AS, Blood loss, cardiac tamponade.
	Pulse ✓ **Rate** ✓ **Rhythm** ✓ **Volume** ✓ Character ✓ Radio femoral delay	✓ **Rate abnormalities → normal PR = 60 – 100 BPM** ▪ **Tachycardia → in response to hypovolemia (like bleeding), anaemia, pain, infection …** ▪ **bradycardia** ✓ **volume abnormalities → normally full** ▪ **feeble pulse (very weak) → hypovolemia --** ▪ **absent (pulse is not palpable) → shock** ▪ **bounding → AR** ✓ **Rhythm abnormalities → normally regular**

	✓ Condition of the vessel (like cording)	▪ **Irregularly irregular → AF** ▪ **Regularly irregular → ectobic beat** ✓ **Pulse deficit → difference between heart beat rate and peripheral arterial rate → AF** ✓ Different characters of pulse → their cause ▪ Water hammer (collapsing pulse)/bounding pulse → AR ▪ Pulsus paradoxus → pericardial tamponade ▪ Pulsus alterans → Advanced CHF ▪ Anacrotic pulse → AS ▪ Bisferense pulse → AR ± AS ▪ Hypokinetic pulse → hypovolemia (constrictive pericarditis, MS), LSHF ▪ Hyperkinetic pulse → Anaemia, thyrotoxicosis, PDA, pregnancy, complete heart block ✓ Radio femoral delay → coarctation of aorta in paediatrics ✓ Cording → DM, dyslipidemia, Aging **PR reporting example** **PR = 72 BPM, regular and full in volume**
	Reporting of normal arterial examination ☛ All accessible peripheral arteries are palpable, full in volume and regular in rhythm	
Venous Examination	**Distended neck vein**	
	JVP	✓ Normal→ 3-4 cm (8-9 mmhg) ✓ Raised JVP → **CHF, constrictive pericarditis, SVC sxx, cardiac tamponade,** rarely in CLD, Nephrotic sxx and obstructive lung disease ✓ +ve kussmauls sign → raised JVP during inspiration ▪ Constrictive pericarditis ▪ rCMP ▪ MI (right ventricular infarction) Clinical features to distinguish jugular from carotid artery pulsations 
	Hepato jugular reflex	✓ +ve in CHF (major criteria of Framingham)
	Reporting of normal venous examination ☛ No distended neck vein, JVP = 3cm	

Internal Jugular Pulsations	Carotid Pulsations
Rarely palpable	Palpable
Soft, rapid, undulating quality, usually with two elevations and two troughs per heart beat	A more vigorous thrust with a single outward component
Pulsations eliminated by light pressure on the vein(s) just above the sternal end of the clavicle	Pulsations not eliminated by this pressure
Level of the pulsations changes with position, dropping as the patient becomes more upright.	Level of the pulsations unchanged by position
Level of the pulsations usually descends with inspiration.	Level of the pulsations not affected by inspiration

Precordial examination

	Examination techniques	Possible abnormal findings and their causes
Inspection	❖ Activity ❖ Apical impulse (AI) ❖ Precordial Buldge ❖ scar	✓ Activity ▪ Active precordium → normal ▪ Hyper active precordium → HCMP, CHF (cardiomegaly) ▪ Quite (silent) precordium → IHD, DCMP, massive pericardial effusion ✓ AI ▪ Normally @ 4th or 5th ICS, @ or medial to left MCL ▪ Not visible → pericardial effusion, constrictive pericarditis, highly muscular individuals ▪ Displaced downwards and laterally → Cardiomegaly of different causes (see below) ✓ Precordial bulge → long standing CHD ✓ Scar → evidence for surgical treatment of CHD
	Reporting format for normal precordial inspection finding ☛ Active precordium, AI @5th ICS medial to left MCL, no precordial buldge or scar	
Palpation	✚ Heart sounds (palpable or not) ✚ PMI ✚ Heave and thrill	✓ Heart sounds ☛ Distant heart sounds → rCMP, Cardiac tamponade ▪ Beck's triad of cardiac tamponade include 1) Distended neck vein 2) Hypotension 3) Distant / muffled heart sounds ☛ Palpable P2 at pulmonary area → Pulmonary HTN ☛ Palpable S2 at aortic area → systemic HTN ✓ PMI ▪ Localized, tapping, non-sustained → normal ▪ Diffuse, thrusting, sustained → LVH 2ry to HTN, AS ☛ Diffuse → palpable by 2nd & 4th finger while 3rd is off from the precordial area, > 2.5cm in size or occupy > 1 ICS ☛ Sustained → occupies more than 2/3rd of cardiac cycle ✓ Heave → indicate cardiomegaly ▪ Left parasternal heave → RVH ▪ Apical heave → LVH ✓ Thrill ▪ Palpable murmur like purring of a cat ▪ Indicate grade 4 and above murmur
	Reporting format for normal precordial palpation finding ☛ Palpable heart sounds, PMI @5th ICS medial to left MCL which is Localized, tapping and non-sustained, no heave or thrill	

Auscultation	✓ S1 & S2 (heart sounds) ✓ Added heart sounds (S3 & S4 gallop) ✓ Murmur ✓ Other heart sounds	✓ Added heart sounds ▪ S3 gallop ✚ Due to rapid ventricular filling in early diastole ✚ Normal finding in athletes ✚ Physiologic S3 occurs in young adults of < 4o age ✚ **Anaemia** ✚ **Thyrotoxicosis** ✚ **CHF** ✚ **CMP** ▪ S4 gallop ✚ Due to vigorous atrial contraction against stiff ventricle ✚ Normal finding in athletes ✚ **HHD** ✚ **AS** ✚ **HCMP** ✓ Other heart sounds ▪ Pericardial friction rub → ARF, acute pericarditis ▪ Pericardial knock → constrictive pericarditis ▪ Opening snap → MS
	Reporting format for normal precordial auscultation finding ☛ S1 & S2 are well heard, no murmur or gallop	

Signs of congested heart failure

1. **GA**
   - Cardiopulmonary distress
   - Edematous
2. **Vital signs**
   - Tachycardia ± Tachypnea
3. **HEENT**
   - Facial puffiness
4. **RS**
   - Basal rales /creptation and other pulmonary edema features
   - Pleural effusion
5. **CVS**
   - Distended neck vein
   - Raised JVP
   - S3 gallop
   - Cardiomegaly
6. **Abdomen**
   - Positive Hepatojugular reflex
   - Tender hepatomegaly
   - Ascites

7. MSS
    - Bilateral pitting edema

1.2.2. Murmur

Murmur characterization

`Mnemonic for rehearsal of murmur characterization components`

GP interprets **QT** interval in **L**ight, **R**apid, & **S**imple **M**ethod

1. Grade

- ✓ Systolic murmurs have 6 grades
    1) Grade I - **faint** murmur, heard only with special efforts
    2) Grade II - **quiet** but heard murmur
    3) Grade III - **moderately loud** murmur
    4) Grade IV - **loud** murmur accompanied by a **thrill**
    5) Grade V - very loud, heard with a **stethoscope partly off** the chest
    6) Grade VI- Heard with the **stethoscope entirely off** the chest
- ✓ Diastolic murmurs have only 4 grades

2. Pitch

- ✓ High
- ✓ Medium
- ✓ Low

3. Quality

- ✓ Blowing → MR, TR, AR
- ✓ Rumbling → MS
- ✓ Harsh
- ✓ Musical

☛ `Rasping → AS`

4. Timing

➔ Identify whether the murmur is **systolic, diastolic or continuous** in comparison to carotid pulse

- ☛ Systolic murmurs coincide with carotid pulse, while the diastolic do not

✓ **Systolic murmurs**

5. Location of maximal intensity → Signifies origin of murmur, shows where the murmur did best heard

- ✓ MR, MS → over the mitral area
- ✓ TR, TS → LLSB
- ✓ AR → erb's point (left 2nd to 4th ICS)
- ✓ AS → right 2nd ICS
- ✓ PR, P2 accentuation → left upper sternal border

6. Radiation → Signifies direction of blood flow

- ✓ MR → to the left axilla/ base of heart
- ✓ AS → to the neck
- ✓ TR → to the epigastrium

7. Shape (configuration) → related to timing and not usually reported in physical examination

- ✓ Crescendo → Murmur grows louder. Eg. Pre-systolic murmur of MS
- ✓ Crescendo-decrescendo → Murmur that grows louder and then fall. Eg. Mid-systolic murmur of AS
- ✓ Decrescendo → Murmur grows softer and slowly falls. Eg. Early diastolic murmur of AR

1. Mid-systolic murmur (MSM)
   - ❖ Begin after S1 and stops before S2
   - ❖ E.g. Murmur of **AS**, PS, ASD
2. Late systolic murmur (LSM)
   - ❖ Starts in mid or late systole and persists up to S2
   - ❖ E.g. Murmur of Mitral valve prolapse (**MVP**)
3. Pansystolic murmur (PSM)
   - ❖ Starts with S1 and stops at S2
   - ❖ E.g. Murmur of **MR, TR, VSD**

✓ **Diastolic murmur**

1) Early diastolic murmur (EDM)
   - ❖ Starts after S2 and fades into silence before next S1
   - ❖ Eg. Murmur of **AR, PR**
2) Mid diastolic murmur (MDM)
   - ❖ Starts after S2 and fade away or merge into a late diastolic murmur
   - ❖ Eg. Murmur of **MS, ASD**
3) Late diastolic (presystolic) murmur (LDM)
   - ❖ Starts late in diastole and continuous up to S1
   - ❖ Eg. Murmur of **TS** in sinus rhythm

✓ **Continuous murmur**

- ❖ Begin in systole, peak at S2, and continue into all or part of diastole
- ❖ Eg. Murmur of **PDA** (continuous machinery like murmur is typical for PDA)

✓ Plateau → Murmur has same intensity throughout. Eg. Pansystolic murmur of MR, TR

8. Manoeuvre

✓ Respiration
- ❖ ***Left***-sided murmurs increase with ***expiration*** → **MR, AR**
- ❖ ***Right*** - sided murmurs increase with ***inspiration*** → **TR, PR**

✓ Positioning → mostly used manoeuvre
- ❖ Tilting forward
  - ☛ Increases the intensity of **AR**
- ❖ Leaning to left lateral position
  - ☛ Increases the intensity of **MS**

✓ Hand grip exercise
- ❖ Increases the intensity of **MR and AR**

✓ Valsalva
- ❖ Standing → **Increases** the intensity of **MR** and **decreases** the intensity of **AS**
- ❖ Squatting → **Increases** the intensity of **AS** and **decreases** the intensity of **MR**

Characteristics of common cardiac valvular lesions

Tip → during physical examination.
- ☛ for Timing → press carotid and Auscultate the murmur simultaneously for comparison
- ☛ for radiation → check possible sites (neck, epigastrium, axilla)
- ☛ do maneuvers for accentuation of murmur

	MR	TR	AR	AS	MS
Grade	Usually III			Usually II to III	
Pitch	Medium to High pitched			Low pitched	
Quality	Blowing			Rasping	Rumbling
Time	Pan systolic murmur		Early diastolic murmur	Mid systolic murmur	Mid diastolic murmur
Location	Best heard at the **Apex of the heart**	Best heard at the **LLSB**	Best heard at the **erb's point**	Best heard at the **aortic area**	**Limited to the apex**
Radiation	to the left axilla/ base of heart	to the epigastrium		to the neck	
Manoeuvre		Accentuated by deep inspiration	Accentuated by leaning forward and expiration		Accentuated by left lateral

					positioning and exercise
Other associated findings	✓ Laterally and down ward displaced AI ✓ Muffled S1 ✓ Prominent S3 gallop		✓ Laterally and down ward displaced AI ✓ Wide pulse pressure ✓ Water hammer pulse ✓ Absent S2	✓ Laterally and down ward displaced AI ✓ Anacrotic arterial pulse	✓ Accentuated S1 ✓ Opening snap following S2
Reporting format	✓ Grade III, High pitched, Blowing, Pansystolic murmur, Best heard at the **Apex of the heart,** which radiates to the left axilla/ base of heart	✓ Grade III, High pitched, Blowing, Pansystolic murmur, Best heard at the LLSB, which radiates to the epigastrium, Accentuated by deep inspiration	✓ Grade III, High pitched, Blowing, early diastolic murmur, Best heard at the erb's point, accentuated by leaning forward and expiration	✓ Grade II, low pitched, rasping, mid systolic murmur, Best heard at the **Aortic area,** which radiates to the neck	✓ Grade II, low pitched, rumbling, mid diastolic murmur, limited to the apex, accentuated by left lateral positioning and exercise
Causes (DDX) Click here → Valvular heart disease (VHD)	❖Acute ○ IE ○ Papillary muscle rupture (Post MI) ○ Chordae tendineae rupture ○ Blunt trauma ❖Chronic ○ Primary MR- ▪ RHD ▪ IE ▪ Mitral valve prolapse (MVP) ▪ Trauma ▪ Congenital (cleft, AV canal) ○ Secondary (functional) MR ▪ IHD ▪ DCMP ▪ HCMP ▪ Chronic	✓ Primary (organic) • Rheumatic fever/RHD • IE • Papillary muscle injury (post-MI) • Myxomatous (tricuspid valve prolapse) • Leaflet trauma • Radiation • Carcinoid heart disease • Endomyocardial fibrosis • CHD in children (Ebstein's malformation of the tricuspid valve) ✓ Secondary (functional) /cause of > 80% of TR/ • MI • Cardiomyopathy (HCMP, DCMP) • Atrial fibrillation (AF) • Longstanding pulmonary HTN • Left-sided valve disease	✓ Acute ○ IE ○ Trauma ○ Aortic dissection ○ Trauma ✓Chronic ○ Primary valvular disease: ▪ Rheumatic fever (RHD) ▪ IE ▪ Congenital Bicuspid aortic valve ▪ SLE ▪ Syphilitic aortitis ▪ Ankylosing spondylitis. ▪ Myxomatous (prolapse) ○ Aortic root disease ✓ Aortic dissection ✓ Systemic severe HTN ✓ Cystic medial degeneration of the ascending	✓ Rheumatic fever or CRMVHD ✓ Congenital (bicuspid, unicuspid) ✓ Degenerative calcification ✓ Radiation	✓ Rheumatic fever/RHD (>95%) ✓ Other less common causes ○ IE ○ Congenital ○ Severe mitral annular calcification with leaflet involvement ○ SLE ○ RA ○ Myxoma

	Atrial Fibrillation ○ Mitral annular calcification		aorta ✓ Marfan syndrome ✓ Bicuspid aortic valve ✓ Nonsyndromic familial aneurysm ✓ Aortitis ✓ Idiopathic dilation of the aorta ✓ Annuloaortic ectasia ✓ Osteogenesis imperfecta		
IX	Refer long case of nitsibin → IX of HF (click here → Chapter 1; Heart failure (ልብ ድካም))				
Mgt principle	Refer long case of nitsibin → mgt of HF (click here → Management of heart failure) and VHD mgt (Click here → Valvular heart disease (VHD))				

N.B

✓ Peripheral signs of AR

- *deMusset's sign* — head bob occurring with each heart beat
- *Traube's sign* — a pistol shot pulse (systolic and diastolic sounds) heard over the femoral arteries
- *Duroziez's sign* — a systolic and diastolic bruit heard when the femoral artery is partially compressed
- *Quincke's pulses* — capillary pulsations in the fingertips or lips
- *Mueller's sign* — systolic pulsations of the uvula
- *Becker's sign* — visible pulsations of the retinal arteries & pupils
- *Hill's sign* — popliteal cuff systolic pressure exceeding brachial pressure by more than 60 mmHg
- *Mayne's sign* — more than a 15 mmHg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position
- *Rosenbach's sign* — systolic pulsations of the liver
- *Gerhard's sign* — systolic pulsations of the spleen

DDX for cardiomegaly

- HHD

- DCMP
- HCMP
- CAD (MI)
- CHD
- Peripartum CMP
- Pulmonary HTN
- Pericardial effusion
- Hemochromatosis
- Amyloidosis
- Idiopathic

DDX for Displaced PMI

- Cardiomegaly of different causes
- Chronic Pleural or pulmonary disease
- Deformities of chest wall or thoracic vertebrae

1.2.3 Leg edema

Pedal and pretibial pitting edema occurs in

- CHF → symmetrical and worsens in the evening and improves early in the morning
- Constrictive pericarditis
- CLD → starts with ascites which may progress to GBS
- Nephrotic syndrome or AKI/CKD → affects face first
- Advanced Lymphoma (NHL)
- Disseminated TB to pericardium (result in Constrictive pericarditis), pleura, Peritoneum…
- Varicose veins and DVT
- Vasodilating drug (e.g. a calcium channel blocker)
-

Edema grading

- ✓ Palpate behind the medial malleolus and the distal shaft of the tibia, and dorsum of foot for pitting edema by gently compressing the area for at least 15 seconds with the thumb

Grade	Grading by body sites (mostly used clinically)	Grading by time to refill the pitting edema	Grading based on compression depth
I	**pedal and pretibial** edema	< 5 seconds	2cm
II	Edema involving **leg and thigh**	5-10 seconds	2 - 4cm
III	Edema involving **abdominal wall and pre-sacrum**	10-15 seconds	4 - 6 cm

IV	**Anasarca** (generalized edema including serosal fluid accumulation)	> 15-20 seconds	> 6 cm

1.3 Abdominal examination

1.3.1 Physical examination findings

Examination techniques		Possible abnormal findings and their causes
N.B. ✓ while doing abdominal examination 1st look at sclera and skin for jaundice (hepatitis) ✓ the order of examination should be Inspection → auscultation → palpation → percussion *(since bowel sounds are affected by palpation, auscultate bowel sound before palpation)*		

Inspection	❖ Symmetry
	  ✓ Movement with respiration
	❖ Shape (check also flank fullness and contour of umbilicus)
	❖ Superficially distended abdominal veins
	❖ Scar
	❖ Straie
	❖ Pigmentation
	❖ Peristalsis
	❖ Hernia sites
	  ✓ Don't forget to ask the pt to cough
		❖ Silent abdomen → generalized peritonitis
		❖ Shape of abdomen
		  ✓ Flat → normal
		  ✓ Scaphoid → diaphragmatic hernia
		  ✓ Distended abdomen → ascites, abdominal mass, HSM, gas (intestinal obstruction)
		  N.B 6F'S in abdominal distension
		    ✚ Fluid → ascites
		    ✚ Feces → incomplete intestinal obstruction
		    ✚ Flatus → complete intestinal obstruction
		    ✚ Fat → obesity
		    ✚ Fetus → pregnancy
		    ✚ Fatal growth → organomegaly, malignancy, AAA (abdominal aorta aneurysm)
		❖ Flank fullness
		  ✓ Full flanks with abdominal distension→ ascites
		  ✓ Full flanks without abdominal distension → Psoas abscess, Hydronephrosis, Perinephric abscess
		❖ Contour of Umbilicus
		  ✓ inverted with circular slit or slightly horizontal → normal
		  ✓ Horizontal slit and everted → huge ascites or mass
		  ✓ Horizontal slit → ascites or bilateral flank mass
		  ✓ Vertical slit → mass
		❖ superficially distended and tortuous abdominal vessels
		  ✓ drain away from palpation during palpation which indicate portal HTN (William Harvey method)
		  ✓ draining towards umbilicus → IVC obstruction
		❖ scar → previous surgery or trauma
		❖ straie alba/atrophica → ascites
		  N.B

<table>
<tr><td rowspan="3"></td><td></td><td>✓ Straie gravidarum→ in pregnancy
✓ Purple straie → cushing sxx
❖ Ecchymosis → herald haemorrhages (intra or retroperitoneal)
❖ Vigorous peristalisis → pyloric stenosis, intestinal obstruction</td></tr>
<tr><td colspan="2">N.B.
Peristalsis and superficially distended veins should be observed sitting on bedside and by using adequate light</td></tr>
<tr><td colspan="2">Reporting format for normal abdomen inspection finding
☛ Symmetrically flat abdomen that moves with respiration, flanks are not full, inverted umbilicus with circular slit, there is no superficially distended abdominal veins, no visible scar, straie, pigmentation or peristalsis, hernia sites are free</td></tr>
<tr><td rowspan="2">Auscultation</td><td>✓ Bowel sounds
✓ Bruit
✓ Friction rub</td><td>✓ Bowel sounds
❖ Normal → 5 - 30 kicks/minute
❖ increased in frequency and noisy → early intestinal obstruction, diarrhoea
❖ reduced then absent → generalized peritonitis, paralyzed ileus
✓ Bruit
❖ Over Abdominal aorta → partial obstruction of aorta
❖ Over renal arteries → renal artery stenosis
❖ Over liver → HCC, alcoholic hepatitis
❖ Over femoral and iliac arteries
✓ Friction rub
❖ Liver → liver tumour
❖ Spleen → splenic infarct</td></tr>
<tr><td colspan="2">Reporting format for normal abdomen auscultation finding
☛ Normoactive bowel sounds (18 kicks/min), no bruit over abdominal aorta, renal arteries, iliac arteries or liver</td></tr>
<tr><td rowspan="3">Palpation</td><td>✚ Superficial
✓ Tenderness
✓ Superficial palpable mass
✚ Deep → Search for
■ Guarding
■ Rigidity
■ Mass
■ Direct / rebound tenderness
■ Organomegaly (liver, spleen, kidney)
■ Ballotable mass in ascites</td><td>✓ Guarding, rigidity, direct/rebound tenderness → acute abdomen (firm and board like in generalized peritonitis)
✓ CVAT → pyelonephritis
✓ Abdominal mass
■ Origin from Abdominal wall → protrudes when pt head lifts up
■ Origin from upper abdomen which doesn't allow finger to pass above the mass → mass from liver, spleen, stomach
■ Origin from lower abdomen which doesn't allow finger to pass below the mass → mass from urinary bladder, upper rectum
■ Origin from RUQ → mass from Liver, right kidney, hepatic flexure of colon</td></tr>
<tr><td colspan="2">N.B
If spleen is not palpable, turn the pt to the right with flexion of left heep and knee then repeat palpation. If still not palpable go to percussion methods (Nixon, castles, troubes)</td></tr>
<tr><td colspan="2">Reporting format for normal abdomen palpation finding
☛ Superficial palpation
No superficial tenderness, no superficially palpable mass
☛ Deep palpation
No direct/rebound tenderness, guarding or rigidity, Liver and spleen are not palpable, kidney is not bimanually palpable bilaterally.</td></tr>
</table>

Percussion	➢ Percussion note ➢ TVLS ✓ Should not be done in right sided pleural effusion and ascites ➢ Spleen percussion methods	➢ Percussion note ✓ Tympanic → normal ✓ Hyper tympanic → gas ✓ Dullness → organomegaly, mass, ascites (associated with shifting dullness and fluid thrill) ➢ TVLS ☛ 10 ± 2 cm → normal ☛ Upper border of liver is palpable at 5th ICS along the right MCL normally ☛ TVLS > 12 cm → hepatomegaly ✚ N.B. you can say hepatomegaly after doing TVLS, before doing TVLS you have to report as *liver is palpable "X" cm below the right costal margin* ☛ TVLS < 8cm → shrunken liver (e.g. advanced cirrhosis)
	Spleen percussion methods **Nixon's method** ✓ Ask the patient to turn to the right side ✓ Begin percussing at the lower level of pulmonary resonance along the left posterior axillary line and proceed diagonally along a perpendicular line towards the lower mid-anterior costal margin ✓ The upper border of dullness is normally 6-8 cm above the costal margin ✓ **Dullness > 8cm suggests splenomegaly** **Castell's method** ✓ Ask the pt to be on supine position ✓ Percuss the lower intercostal space at 8th or 9th interspace along left anterior axillary line during full inspiration and expiration ✓ **Dullness on full inspiration suggests splenomegaly** **Traube's method** ✓ Borders of Traube's space: 1. Superiorly 6th rib 2. laterally left mid axillary line 3. inferiorly left costal margin ✓ Ask the patient to be on supine position with the left arm slightly abducted ✓ Percuss from medial to lateral margins in normal breathing. It usually produces normal resonant sound at traube's space ✓ **Dullness to percussion at Traube's space suggests splenomegaly**	
	Reporting format for normal abdomen percussion finding ☛ Tympanic percussion note all over the abdomen, no shifting dullness or fluid thrill, TVLS = 10cm	
	N.B DRE (digital rectal examination) Finally, it is important to do DRE since abdominal examination without DRE is incomplete	

1.3.2 Ascites

Findings	DDX	IX	Mgt principle

✓ symmetrically distended abdomen
▪ flanks are full
▪ eversion of umbilicus with transverse or circular slit
▪ fluid thrill and shifting dullness
▪ superficially distended and tortuous abdominal vessels
    ▪ drain away from umbilicus during palpation which indicate portal HTN (William Harvey method)
▪ straie alba/atrophica
■ associated ballotable mass (e.g. HSM)
	Transudative
	✚ CLD → refer secondary causes from long case of nitsibin (under DDX of CLD)
	✚ RSHF
	✚ Constrictive pericarditis
	✚ Nephrotic sxx (NS), AKI, CKD
	✚ Chronic pancreatitis
	✚ SLE
	✚ Meig's sxx → ovarian ca + pleural and peritoneal effusion
	✚ IVC sxx
	✚ Hypothyroidism → rare
	✚ PLE (protein losing enteropathy) → very rare condition
	Exudative
	✚ Infectious → TB peritonitis
	✚ Malignancy (carcinomatous infiltration) → lymphoma, leukaemia
		✚ Ascitic fluid analysis
		✚ LFT and liver enzymes
		✚ Viral markers (HB$_s$Ag for screening)
		✚ CXR, ECG, ECHO → RSHF
		✚ U/A → NS
			❖ Salt restriction: < 2g per day
			❖ Diuretics:
			    a. Spironolactone 100-200mg/day, escalate to a max. dose of 400-600mg/day.
			    b. Furosemude(lasix) 40-80mg /day, escalate to a max. dose of 120-160mg/day.
			If ascites is still present despite the above measurements, it is defined as ***refractory ascites.***
			❖ Alternative treatment modalities include:
			    1) large-volume paracentesis (therapeutic tap)
			    2) TIPS (trans jugular intra hepatic portosystemic shunt) procedure
			    3) Liver transplant

Reporting format of asites

❖ **Inspection**

Symmetrically distended abdomen that moves with respiration, flanks are full, everted umbilicus with circular slit, there are superficially distended abdominal veins which drain away from umbilicus during palpation, no visible scar, straie, pigmentation or peristalsis, hernia sites are free

❖ **Auscultation**

Normoactive bowel sounds (18 kicks/min), no bruit over abdominal aorta, renal arteries, iliac arteries or liver

❖ **Palpation**

Superficial palpation

No superficial tenderness, no superficially palpable mass

Deep palpation

No direct/rebound tenderness, guarding or rigidity, no ballotable organ

❖ **Percussion**

There is dullness over the flanks, there is shifting dullness but no fluid thrill, TVLS = 10cm

1.3.3 Splenomegally

Findings (characterization)	DDX	IX	Mgt principle

Size → enlarged/palpable mass over the LUQ which is ''X'' cm from left costal margin along the splenic growth line. Tenderness → non tender (if tender consider → splenic abscess, malignancy /e.g. blast crisis phase of CML/) Consistency → soft/firm/hard Surface → smooth Border → sharp edge Palpable medial notch Doesn't allow finger to pass below left costal margin Moves with respiration Not bimanually palpable	Massive	Tipped	RK 39 Splenic aspiration HBsAg CBC & PM BM aspiration Abdominal U/S	
	VL CML, CLL NHL HMS HSS Auto immune haemolytic anaemia Hairy cell leukaemia Thalassemia Goucher disease Niemann pick disease	Military TB IE Malaria SLE Typhus / typhoid fever Sepsis IM (infectious mononucleosis) Brucellosis		

N.B

- Splenomegaly
  - Tipped → 1 - 2 cm
  - Moderate → 3 - 7 cm
  - Massive → ≥ 8 cm
- Hypersplenism
  - Splenomegaly +
  - Pancytopenia +
  - Normocellular BM +
  - Correction of smx by splenectomy (normal post splenectomy cell count)

Reporting format of Splenomegaly

- Enlarged/palpable mass over the LUQ which is ''X'' cm from left costal margin along the splenic growth line, non-tender, firm in consistency, smooth surface, sharp edge, Palpable medial notch, Doesn't allow finger to pass below left costal margin, Moves with respiration, Not bimanually palpable

How to differentiate splenomegaly from enlarged left kidney?

Splenomegaly	Enlarged left kidney
Grows along the splenic growth line Has medial notch Unable to go beneath the costal margin Not bimanually palpable Dull to percussion Moves with respiration	Grows antero-posteriorly Has no medial notch Able to go beneath the costal margin Bimanually palpable but not always Colonic resonance to percussion Moves with respiration

1.3.4 Hepatomegaly, Hepatomegaly with ascites, Hepatosplenomegaly

<table>
<tr><th rowspan="2">Findings (characterization)</th><th colspan="3">DDX</th><th rowspan="2">IX</th><th rowspan="2">Mgt principles</th></tr>
<tr><th>Hepatomegaly</th><th>Hepatosplenomegaly</th><th>Hepatomegaly with ascites</th></tr>
<tr>
<td rowspan="2">Size → enlarged/palpable mass over the RUQ which is ''X'' cm below the right costal margin.
Tenderness → non tender (if tender consider → cardiac congestion of liver
Consistency → soft/firm/hard
Surface → smooth
Edge → blunted in case of cardiac congestion and sharp edge for other causes
Doesn't allow finger to pass below right costal margin
Moves with respiration
Not bimanually palpable</td>
<td>CHF, Constrictive pericarditis
CLD
HCC
Pyogenic liver abscess
VL
Malaria
Typhus / typhoid fever
IM
Brucellosis</td>
<td>CLD
CML, CLL
NHL
HMS
HSS
CHF
VL
Military TB
Chronic Anaemia (haemolytic anaemia, Megaloblastic anaemia)
SLE
Acute retroviral SXX of RVI
IM (infectious mononucleosis)
Brucellosis
Goucher disease
Amyloidosis</td>
<td>1. NHL
2. CML
3. CLD</td>
<td rowspan="2">LFT, viral markers
RK39
CBC & PM
Ascitic fluid analysis→ if there is ascites
Abdominal U/S</td>
<td rowspan="2">✓</td>
</tr>
<tr><td colspan="3">Tender hepatomegaly
➔ Congested liver from CHF, Constrictive pericarditis, Pericardial effusion
➔ Amoebic liver abscess
➔ Acute viral hepatitis
➔ Infected hydatid cyst</td></tr>
<tr><td colspan="6">Reporting format of Hepatomegaly
☛ Enlarged/palpable mass over the RUQ which is ''X'' cm below the right costal margin, non-tender, firm in consistency, smooth surface, sharp edge, doesn't allow finger to pass below left costal margin, Moves with respiration, Not bimanually palpable</td></tr>
</table>

1.3.5 Renomegaly

Findings (characterization)	DDX	IX	Mgt principle

Size → bimanually palpable mass over the left/right lower part of abdomen Tenderness → non tender Consistency → soft/firm/hard Surface → smooth Moves with respiration	HIVAN (HIV associated nephropathy) DM nephropathy PCKD Hydronephrosis Huge pyelonephritis Malignancy (RCC) Amyloidosis Obstructive uropathy (e.g pelvic ureteral junction obstruction)	RFT Abdominal U/S CBC PICT RBS	

1.3.6 Abdominal mass

Findings (characterization)	DDX
Site/ location ☛ Specify the quadrant ☛ Is it abdominal wall or intra-abdominal mass? ▪ Feel the mass while the pt lifts her/his head and shoulders off the pillow to tense the abdominal wall ➢ prominently protruded mass - abdominal wall mass ➢ if the mass disappears- intra-abdominal mass ☛ Identify whether abdominal or pelvic origin **Size &shape** **Surface, edge &consistency** ☛ hard, irregular and nodular → likely *malignant* ☛ regular, round, smooth, tense swelling → likely *cystic* ☛ solid, ill-defined and tender mass suggests an inflammatory lesion **Mobility & attachment** ☛ mass arising from the liver, spleen, kidneys, gall bladder and stomach moves down ward during inspiration ☛ mass arising from the small bowel, transverse colon, mesentery and greater omentum are not usually influenced by respiratory movement ☛ Side-to-side movable lower abdominal mass favours swelling of uterine origin but not from urinary bladder arising mass ☛ completely fixed mass suggests → retroperitoneal origin, advanced tumour, mass resulting from severe chronic inflammation involving other organs (e.g. diverticulitis of the sigmoid colon or a tuberculous ileo caecal mass). **Bimanually palpable or pulsatile** ☛ Pulsatile and expansile abdominal mass favors abdominal aneurysm	Organomegaly NHL Appendiceal mass Appendiceal abscess Malignancy arising from stomach and intestine HCC PCKD AAA (Abdominal aortic aneurism) Hydronephrosis Perinephric abscess Psoas abscess Ovarian mass Myoma

1.4 Nervous system

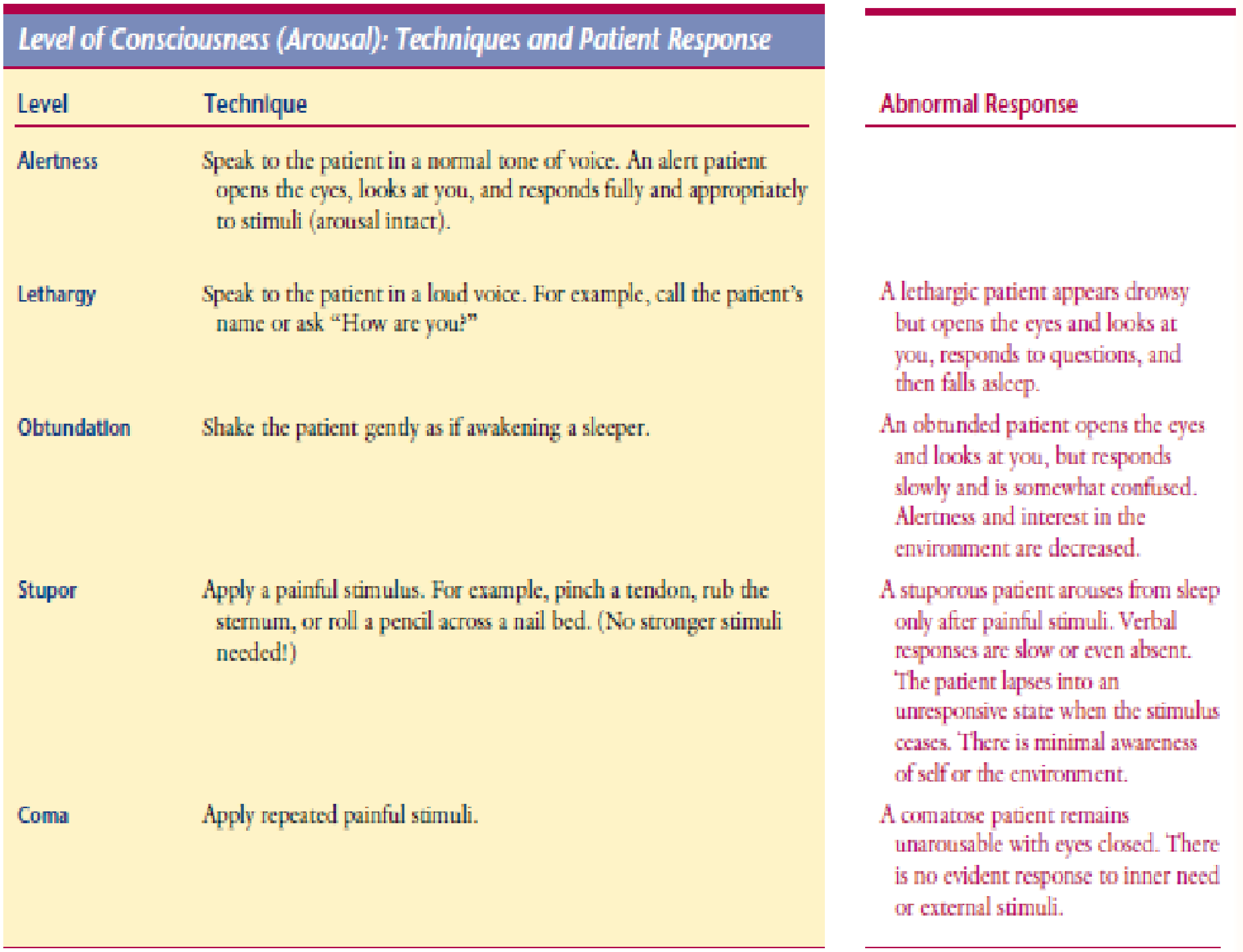
- You may be asked the following in NS examination
  - Do lower motor examination → most cmnly asked
  - Do nervous system examination

1.4.1 Physical examination findings

<table>
<tr><td colspan="6">**Examination techniques**</td><td>**Possible abnormal findings and their causes**</td></tr>
<tr><td colspan="7">**GCS = Glasgow coma scale**</td></tr>
<tr><td rowspan="10">**GCS and FOUR score**</td><td>**Eye opening**</td><td>**Best verbal response**</td><td colspan="2">**Best motor response**</td><td>score</td><td rowspan="7">The GCS is scored between 3 and 15
GCS
≥ 13 → mild brain injury
9 - 12 → moderate brain injury
≤ 8 → severe brain injury.</td></tr>
<tr><td></td><td></td><td colspan="2">**Obeys commands**</td><td>**6**</td></tr>
<tr><td></td><td>**Oriented**</td><td colspan="2">**Localizing** response to pain</td><td>**5**</td></tr>
<tr><td>**Spontaneous**</td><td>**Confused**</td><td colspan="2">**Withdrawal** response to pain</td><td>**4**</td></tr>
<tr><td>Response to **verbal** command</td><td>**Inappropriate words**</td><td colspan="2">**Flexion** to pain</td><td>**3**</td></tr>
<tr><td>Response to **pain**</td><td>Incomprehensible **sounds**</td><td colspan="2">**Extension** to pain</td><td>**2**</td></tr>
<tr><td>**No** eye opening</td><td>**No** verbal response</td><td colspan="2">**No** motor response</td><td>**1**</td></tr>
<tr><td colspan="6">**FOUR score** = Full Outline of Unresponsiveness.</td></tr>
<tr><td>**Eye response**</td><td>**Motor response**</td><td>**Brainstem reflexes**</td><td>**Respiration**</td><td>**score**</td><td rowspan="2">have greater utility than the GCS in coma diagnosis, primarily by including a brainstem examination</td></tr>
<tr><td>eyelids open or opened, tracking, or</td><td>thumbs-up, fist, or peace sign</td><td>pupil and corneal reflexes present</td><td>not intubated, regular</td><td>**4**</td></tr>
</table>

	blinking to command			breathing pattern	
	eyelids open but not tracking	localizing to pain	one pupil wide and fixed	not intubated, Cheyne-Stokes breathing pattern	3
	eyelids closed but open to loud voice	flexion response to pain	pupil or corneal reflexes absent	not intubated, irregular breathing	2
	eyelids closed but open to pain	extension response to pain	pupil and corneal reflexes absent	breathes above ventilator rate	1
	eyelids remain closed with pain	no response to pain or generalized myoclonus status	absent pupil, corneal, and cough reflex	breathes at ventilator rate or apnea	0

Conventional method of assessing level of consciousness



Level of Consciousness (Arousal): Techniques and Patient Response

Level	Technique	Abnormal Response
Alertness	Speak to the patient in a normal tone of voice. An alert patient opens the eyes, looks at you, and responds fully and appropriately to stimuli (arousal intact).	
Lethargy	Speak to the patient in a loud voice. For example, call the patient's name or ask "How are you?"	A lethargic patient appears drowsy but opens the eyes and looks at you, responds to questions, and then falls asleep.
Obtundation	Shake the patient gently as if awakening a sleeper.	An obtunded patient opens the eyes and looks at you, but responds slowly and is somewhat confused. Alertness and interest in the environment are decreased.
Stupor	Apply a painful stimulus. For example, pinch a tendon, rub the sternum, or roll a pencil across a nail bed. (No stronger stimuli needed!)	A stuporous patient arouses from sleep only after painful stimuli. Verbal responses are slow or even absent. The patient lapses into an unresponsive state when the stimulus ceases. There is minimal awareness of self or the environment.
Coma	Apply repeated painful stimuli.	A comatose patient remains unarousable with eyes closed. There is no evident response to inner need or external stimuli.

	Procedure		score
MMSE	A. OREINTATION	Day, Date, Month, Season, Year	5
		Country, State, City, Hospital, Floor	5
	B. REGISTRATION	Name 3 objects and patient repeats	3
	C. ATTENTION & CALCULATION	Serial 7s or spell backwards	5
	D. RECALL	Repeat the 3 objects mentioned before	3
	E. LANGUAGE	Name a pen and a pencil (2points)	9
		Buts' or ifs' (1point)	
		Follow 3 stage command (3points)	
		Read and obey (1point)	
		Write sentence and copy design (2)	

- Mini-mental state examination (MMSE) indicates severity of cognitive impairment
- It is scored out of 30
- MMSE numerical value < 23/30 indicates presence of impaired cognition (dementia)
  - Mild dementia → 21-23/30
  - Moderate dementia → 18-21/30
  - Severe dementia <18/30
- Examples of Buts' or ifs'
  - Betty bought a better butter to make a bitter butter a better butter
  - Don't promise a promise, if you promise keep your promise a promise
  - በበግ ቤት በግ ገባ
  - ጫላ ጩቤ ጨበጠ

CN

CN examination procedures

- CN I → Patency, odour
- CN II → acuity, field, pupillary reaction to light and accommodation
- CN III, IV, VI → Extraocular eye movement
- CN V
  - Temporal and masseter muscle strength
  - Pain and light touch reflex of face
  - Corneal reflex
- CN VII
  - Facial drop or asymmetry
  - Can raise eyebrows or not
  - Open/close eyes against resistance
  - Smile, frown
  - Show teeth
  - Puff out cheeks
- CN VIII
  - Can hear finger rub
  - Rinne and weber test if possible
- CN IX & X
  - Listen patients voice
  - Ask to swallow
  - Ask to say ''AH'' and check location of uveola
  - Check gag reflex
- CN XI
  - Check atrophy/asymmetry of trapezius
  - Can shrug shoulder against resistance
  - Can turn his/her head against resistance
- CN XII
  - Listen articulation of words
  - Tongue inspection
  - Can protrude tongue
  - Can move tongue from side to side
  - Push cheeks by tongue

Motor examination

- **Inspection**
  - position of the extremities after repositioning by the examiner
    - outward rotation → flaccid paresis/plegia
    - inward rotation → spastic paresis/plegia
  - fasciculation
  - Muscle Symmetry → compare proximal with distal, left with right
  - Atrophy
- **Palpation**
  - **Tone**
  - **Power**
  - **Reflex**
    - **DTR ± Clonus, janderasik manoeuvre**
    - **Superficial**
      - **Plantar**
      - Abdominal
      - Scapular
      - Anal
      - Bulbocavernosus
      - Cremasteric
      - Corneal
  - Arm drift
    - Pronator Drift
    - Cerebellar drift
    - Parietal drift
  - Coordination
    - Rapid Alternating Movements
      - ✓ strike one hand on the thigh, raise the hand, turn it over
      - ✓ tap the distal thumb with the tip of the index finger
      - ✓ tap your hand with the ball of each foot
    - Point-to-Point Movements
      - ✓ finger-to- nose test
      - ✓ Heel-to-Shin test
  - Gait
    - Walk across the room, turn and come back
    - Walk heel-to-toe in a straight line (tandem walk)
    - Walk on their toes in a straight line
    - Walk on their heels in a straight line
    - Hop in place on each foot
    - Do shallow knee bend
    - Rise from a sitting position

TONE

- ✓ Can be normotonic, hypotonic (in flacid lesions) or hypertonic (in spastic lesions)

Types of spasticity

1. **Klasp-knife spasticity**: velocity-dependent spasticity with **sudden release after reaching a maximum**, commonly seen in pyramidal tract lesions
2. **Lead-pipe spasticity:** Increased tone present **throughout** the range of motion is observed in frontal lobe disease
3. **Cogwheel spasticity:** Spasticity **enterwined by tremor**, commonly seen in extrapyramidal lesions

- POWER

Grade	Description
0/5	**No** muscle movement
1/5	Visible **flicker** muscle movement, but no movement at the joint
2/5	Movement at the joint **(horizontal mov't),** but not against gravity
3/5	Movement **against gravity**, but not against added resistance
4/5	Movement against resistance, but **less than normal**
5/5	**Normal** strength

- Power interpretation
  - 0/5 & 1/5 → plegia
  - 2/5 - 4/5 → paresis
  - 5/5 → normal

DTR Grading Scale

Grade	**Description**
0	Absent (with Jendrasik maneuver)
1+ or +	Hypoactive (less brisk)
2+ or ++	"Normal" (brisk)
3+ or +++	Hyperactive without clonus (very brisk)
4+ or ++++	Hyperactive with clonus

Difference between UMNL and LMNL

Variables	LMN lesion	UMN lesion
Fasciculation	Present	absent
Atrophy	Present	none, mild
Tone	Hypotonia	hypertonia
Reflex	hyporeflexia	hyperreflexia

Plantar reflex	No response	Up going/Babinski +ve

Plantar reflexces
- ✓ Upgoing /babniski +ve → normal or UMNL
- ✓ Down going
- ✓ No response / equivocal → LMNL

Sensory examination	❖ **Primary sensory test** ☛ Pain, temperature, light touch → test for anterolateral tract ☛ Position and vibration → test for posterior tract ❖ **Cortical sensory test** ☛ Extinction or simultanagnosia ☛ Graphesthesia ☛ Stereognosis ☛ Two Point Discrimination ☛ Double simultaneous stimulation (DSS)	Positive sensory phenomena by neurologic examination ✓ Hypesthesia/hypoesthesia ✓ Anesthesia ✓ Hypalgesia ✓ Hyperesthesia ✓ Allodynia ✓ Hyperalgesia ✓ Hyperpathia Negative sensory phenomena by neurologic examination ✓ Impaired or absent primary sensory modalities like to touch, vibration, position, and temperature
Meningea	❖ Signs of meningeal irritation ☛ **Neck stiffness** ☛ **Kernig's sign** ☛ **Brudzinski's sign** ☛ Jolt accentuation of headache	

Reporting format for normal NS Examination finding

- ☛ Level of consciousness
- ➢ GCS = 15/15 (E4V5M6), conscious and alert
- ☛ CN examination
- ➢ **CN-I:**
    - S/he can smell soap via each nostril.
- ➢ **CN-II:**
    - S/he can differentiate 2 fingers at about 6 meters. (Visual Acuity)
    - S/he sees waggling of finger approximately 1000 from axis of eye. (Visual Fields)
    - S/he differentiates green and red colours. (Colour Appreciation)
    - Normal direct and consensual pupillary light reflex
- ➢ **CN-III, IV & VI:**
    - The eyes can move in all directions. There is no nystagmus or diplopia. The pupils are round, regular in outline and equal in size. They react to light directly and consensually.
- ➢ **CN-V:**
    - S/he identifies light touch and pin prick over the mandibular, maxillary and ophthalmic areas of the face.
    - S/he closes her/his eyes at the touch of the cornea with a cotton swab.
    - Contraction of the temporal and masseter muscles is symmetrical and strong while clenching her/his teeth.
- ➢ **CN-VII:**
    - The face is symmetrical at rest and during voluntary movements (smiling, frowning).
    - S/he can smile, frown her/his forehead, puff out her/his cheeks
    - can close both eyes equally and forcefully against resistance.
    - Intact nasolabial fold
    - Intact corneal reflex

- **CN-VIII:**
    - S/he can hear rubbing of the fingers on both ears.
- **CN-IX & X:**
    - The soft palate rises in the midline when saying 'ah!
    - Centrally located uvula
    - S/he can swallow his saliva
- **CN-XI:**
    - The Sternocleidomastoid and trapezius muscles contract on turning the head and on shrugging the shoulder against resistance, respectively
- **CN-XII:**
    - The tongue protrudes in the midline and shows no fasciculation or atrophy.

- Motor examination
    - Inspection
        - The limbs are centrally positioned, no inward or outward rotation
        - Comparable muscle bulk between the left and the right side of both upper and lower extremities.
        - There is no spontaneous as well as induced fasciculation.
    - Palpation
        - Tone and power

	TONE		POWER	
	Upper	Lower	Upper	Lower
Right	Normo-tonic	Normo-tonic	5/5	5/5
Left	Normo-tonic	Normo-tonic	5/5	5/5

- Reflexes
    - Superficial
        - Abdominal reflex is present both in upper and lower quadrants.
        - Corneal reflex is intact in both eyes.
        - Plantar reflex is down going on both sides.
    - DTR

	Biceps	Triceps	Brachioradialis	Patellar	Ankle
Right	++	++	++	++	++
Left	++	++	++	++	++

- Sensory examination
    - Primary sensory exam
        - S/he identifies light touch and pin prick over the extremities and trunk.
        - S/he is able to recognize different movements of the toes with his eyes closed. (Position sense)
        - Vibration sense was not assessed due to lack of Tuning Fork.
    - Cortical sensory exam
        - S/he appreciates the form of a key by means of only touch (Stereognosis)
        - S/he recognizes writings of different numbers on his palm (Graphesthesia)
        - S/he is able to differentiate 2 pin pricks up to 4 mm apart over the finger tips (2 pt discrimination).
- Coordination
    - Finger to nose, heal to shin and rapid alternating movement of the arm were done without any abnormalities.
- Meningeal irritation signs
    - No neck stiffness.
    - Kernig's Sign is negative.
    - Brudzinski's Sign is negative

1.4.2 Paraplegia/paresis

Refer long case of nitsbin (click here → Chapter 7; Paraplegia (ከወገብ በታች ሽባነት))

1.4.3 Monoplegia/paresis

Findings	DDX			IX	Mgt principle
	UL only	LL only	Both UL and LL		
✓ position of the extremities after repositioning by the examiner ☛ outward rotation → flaccid paresis/plegia ☛ inward rotation → spastic paresis/plegia ✚ Decreased muscle bulk of the affected limb ✚ spontaneous as well as induced fasciculation in LMNL Cases ✚ hypertonic in spastic lesions and hypotonic in flacid lesions ✚ power 0/5 & 1/5 in plegia, 2/5 upto 4/5 in paresis ✚ hyperreflexia in UMNL and hyporeflexia in LMNL ✚ plantar reflex ☛ Upgoing /babniski +ve → normal or UMNL ☛ Down going/No response / equivocal → LMNL ✚ Absent primary and cortical sensory tests on the affected limb	✚ Brachial plexopathy	✚ Lumbosacral plexopathy ✚ Cauda equina sxx	✚ TIA ✚ Poliomyelitis ☛ Cause radiculopathy ✚ Vasculitis ✚ BSS (Hemi section of the cord) ✚ Early stage of foramen magnum sxx ☛ Clock wise rotation of weakness	✚ Refer long case of nitsbin under paraplegia	

1.4.4 Quadriplegia/paresis

Findings	DDX	IX	Mgt principle
✓ position of the extremities after repositioning by the examiner ☛ outward rotation → flaccid paresis/plegia ☛ inward rotation → spastic paresis/plegia ✚ Decreased muscle bulk of all 4 extremities ✚ hypertonic in spastic lesions and hypotonic in flaccid lesions ✚ power 0/5 & 1/5 in plegia, 2/5 upto 4/5 in paresis ✚ hyperreflexia ✚ plantar reflex → Upgoing /babniski +ve ✚ Absent primary and cortical sensory tests in all 4 extremities	✚ Foramen magnum sxx ✚ Cervical cord lesions (e.g. craniovertebral anomaly, trauma to cervical cord) ✚ TM of cervical cord ✚ GBS ✚ Bilateral brainstem lesions ✚ Central cord sxx involving cervical cord ✚ Anterior spinal artery sxx involving cervical cord ✚ Poliomyelitis ✚ MS ✚ MND ✚ Peripheral neuropathy	✚ Refer long case of nitsbin under paraplegia	

1.4.5 Coma

DDX			IX	Mgt principle
Symmetrical, nonstructural	**Symmetrical, structural**	**Asymmetrical, structural**		
✚ Metabolic ☛ Hypoglycemia ☛ **DKA** ☛ **Lactic acidosis** ☛ **Hyperglycemic nonketotic coma** ☛ **Hepatic encephalopathy** ☛ **Uremia** ☛ **Hypertensive encephalopathy** ☛ Wernicke encephalopathy ☛ Dialysis encephalopathy ☛ **Hypoxia** ☛ Hypercapnia ☛ Hyper/hypothermia ☛ Hypernatremia	✚ Supratentorial ☛ **Sagittal sinus thrombosis** ☛ **SAH** ☛ **Trauma-** contusion, concussion ☛ Bilateral internal carotid occlusion ☛ Bilateral anterior cerebral artery occlusion ☛ Thalamic hemorrhage ☛ Hydrocephalus ✚ Infratentorial ☛ **Midline brainstem tumor** ☛ Basilar occlusion	✚ Supratentorial ☛ **SDH** ☛ **Bilateral ICH** ☛ **Subdural empyema** ☛ **Thrombophlebitis** ☛ **Unilateral hemispheric mass (tumor, abscess, bleed) with herniation** ☛ **Cerebral vasculitis** ☛ **Cerebral abscess** ☛ **TTP** ☛ **DIC** ☛ Multiple sclerosis ☛ Acute disseminated encephalomyelitis	✚ **Screening laboratories** (CBC, RBS, electrolytes, BUN, creatinine, PT, PTT, ABG, LFTs, drug screen) ✚ **ECG** ✚ **Head CT scan** → prioritize emergent if focal neurologic signs, papilledema, fever ✚ **LP** → prioritize emergent after CT scan if fever, elevated WBC, meningismus; otherwise do according to level of suspicion for diagnosis or	✚ **ABCs:** ☛ Secure IV line ☛ Intubate if GCS ≤8 ☛ Stabilize C Spine ☛ Supplement O2 ☛ Blood pressure support as needed ✚ **Glucose** 50 percent IV 50 mL (after blood drawn, before results back) ✚ Consider **empiric treatments:** ☛ For possible infection → Ceftriaxone and

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☛ Hyper/hypocalcemia ☛ Hypermagnesemia ☛ Hypothyroidism ☛ Reye syndrome ☛ Aminoacidemia ☛ Porphyria ☛ Addisonian crisis ✚ Infections ☛ **Bacterial meningitis** ☛ **Viral encephalitis** ☛ **Cerebral Malaria** ☛ **Postinfectious encephalomyelitis** ☛ Waterhouse-Friderichsen syndrome ☛ Syphilis ☛ Sepsis ☛ Typhoid fever ✚ Toxins ☛ Lead ☛ **Methanol** ☛ **Ethylene glycol** ☛ **Carbon monoxide** ☛ **Mushrooms** ☛ Thallium	☛ Pontine hemorrhage ☛ Central pontine myelinolysis	☛ Subacute bacterial endocarditis ☛ Nonbacterial thrombotic endocarditis (marantic endocarditis) ☛ Multifocal leukoencephalopathy ☛ Pituitary apoplexy ☛ Massive or bilateral supratentorial infarction ☛ Creutzfeldt-Jakob disease ☛ Adrenal leukodystrophy ☛ Leukoencephalopathy associated with chemotherapy ✚ Infratentorial ☛ Brainstem infarction ☛ Brainstem hemorrhage ☛ Brainstem thrombencephalitis	if cause remains obscure ✚ **Other laboratory tests** → blood cultures, adrenal and thyroid tests, coagulation tests, carboxyhemoglobin, specific drug concentrations - do according to level of suspicion for diagnosis or if cause remains obscure ✚ **Brain MRI** with DWI, if cause remains obscure ✚ **EEG:** for possible nonconvulsive seizure, or if diagnosis remains obscure	Vancomycin, acyclovir ☛ For possible ingestion→ Naloxone, Flumazenil, Gastric lavage/activated charcoal ☛ For possible increased ICP → mannitol ☛ For possible nonconvulsive status→ Lorazepam, Phenytoin or equivalent ✚ **Treat definite seizures** with phenytoin or equivalent ✚ **Thiamine 100 mg IV**
	Comma mimetics			

☛ Cyanide ✚ Drugs ☛ **Sedatives** ☛ **Barbiturates** ☛ **Alcohol** ☛ **Opiates** ☛ **Salicylate** ☛ Anticholinergics ☛ Amphetamines ☛ Psychotropics ☛ Lithium ☛ Phencyclidine ☛ Other hypnotics ☛ Tranquilizers ☛ Bromides ☛ Paraldehyde ☛ Monoamine oxidase inhibitors ✚ Psychiatric ☛ Catatonia ✚ Other ☛ Postictal seizure ☛ **Diffuse ischemia (myocardial infarction, heart failure, arrhythmia)** ☛ **Hypotension** ☛ **Fat embolism** ☛ Nonconvulsive status epilepticus ☛ Heat stroke	✚ **Locked-in syndrome** ☛ Consciousness is preserved; however, the patient cannot move muscles in the limbs, trunk, or face, except that voluntary blinking and vertical eye movements remain intact. ☛ It is a consequence of a focal injury to the base of the pons, usually by embolic occlusion of the basilar artery ✚ **Akinetic mutism** ☛ The patient follows with the eyes but does not initiate other movements or obey commands. The patient's tone, reflexes (including response to cold caloric stimulation), and postural reflexes usually remain intact ☛ A lack of motor response in an awake individual might arise from injury to the prefrontal or premotor (including supplementary motor) areas responsible for initiating movements ✚ **Psychogenic unresponsiveness** ☛ Patients with psychogenic unresponsiveness often resist passive eye opening, roll over when tickled to avoid the stimulus, turn the eyes towards the floor regardless of which side they are lying on, or demonstrate nonepileptic seizures ☛ The presence of nystagmus with caloric stimulation in an apparently comatose patient supports a diagnosis of psychogenic unresponsiveness, but is not perfectly specific for this diagnosis		

1.5 HEENT

1.5.1 physical Examination findings

1.5.2 Icteric sclera

The differential diagnosis for yellowing of the skin is limited. It includes:

- **Jaundice** → refer under long case of nitsibin (discussion section of CLD)
- The use of the drug **quinacrine**

- Excessive exposure to **phenols**
- Carotenoderma → It occurs in healthy individuals who ingest excessive amounts of vegetables and fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches, and oranges.
    - **Carotenoderma can be distinguished from jaundice by the sparing of the sclerae.**

Pale conjunctiva

1.6 LGS

1.6.1 physical Examination findings

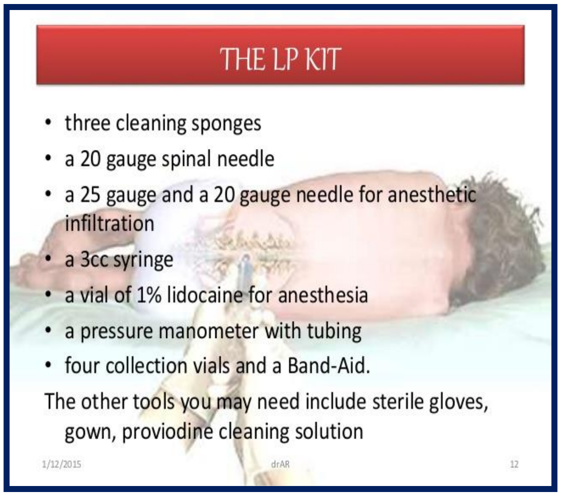
1.6.2 LAP

Chapter 2; common medical procedures and result analysis

Dr. Mulualem. G

2.1 LP (Lumbar puncture)

Indications	Contra indications	CXN
✢ DIAGNOSIS ☛ **CNS infection** (meningitis, encephalitis…) ☛ SAH ☛ NPH ☛ CNS/PNS Demyelinating disorders ☛ CNS Inflammatory disorders ✢ Therapeutic ☛ **Therapeutic LP for cryptococcal meningitis** → Control of raised ICP: daily LP with withdrawal of 20-30ml of CSF ☛ For communicating hydrocephalus and NPH ☛ Treatment of Idiopathic ICP ☛ Spinal artery ischemia ✢ Others ☛ Infusion of **anesthesia** and **Intra-thecal chemotherapy** ☛ **Instillation of contrast** like CT myelography, cisternography	✢ ABSOLUTE ☛ Clinical evidences of increased ICP due to CNS mass or obstructive Hydrocephalus. ☛ CT evidence of shift ☛ Active Bleeding disorders ☛ Skin infection at LP site ✢ RELATIVE ☛ Respiratory pattern like RDS ☛ HTN, Bradycardia with LOC ☛ Acute spinal trauma and vertebral deformity ☛ LOC with hypotension ☛ Status epilepticus	✢ Post puncture headache ✢ Epidermoid tumour ✢ Infection ✢ Cerebral herniation ✢ Spinal Hematoma



THE LP KIT

- three cleaning sponges
- a 20 gauge spinal needle
- a 25 gauge and a 20 gauge needle for anesthetic infiltration
- a 3cc syringe
- a vial of 1% lidocaine for anesthesia
- a pressure manometer with tubing
- four collection vials and a Band-Aid.

The other tools you may need include sterile gloves, gown, proviodine cleaning solution

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Lumbar Puncture

Positioning

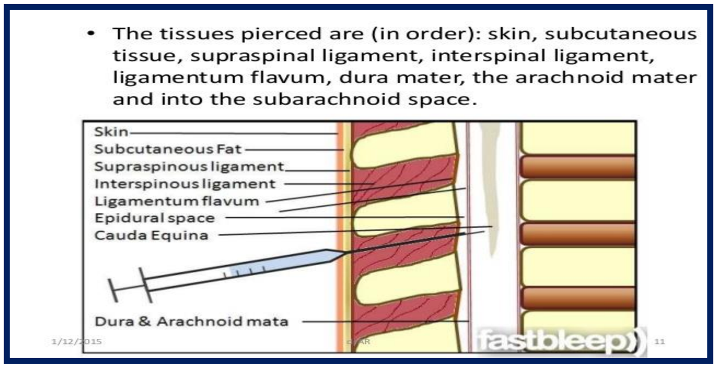
- ✓ Positioning depends on what is required from LP
- ✓ To increase yield use sitting posture
- ✓ For treatment purpose use sitting posture
- ✓ To reduce post LP headache, use fetal posture
- ✓ To measure CSF pressure, use fetal posture

- L3-L4, L4-L5, and L5-S1 interspaces are appropriate for needle puncture. These interspaces can be identified via palpation of bony landmarks

Procedure

- Cleanse skin with povidone iodine from puncture site radially out to 10cm to allow to dry
- Drape below patient and around site with fenestrated drape
- Anesthetize with lidocaine if topical not used by
  - ✓ Intradermally raising a wheal at needle insertion site
  - ✓ Advance needle through wheal to desired interspace → careful not to inject into a blood vessel or spinal canal
- Insert spinal needle with stylet with bevel up to keep cutting edge parallel with nerve and ligament fibers

- LP: Resulting in a “pop” with sudden decrease in resistance when the dura is pierced and the subarachnoid space is entered



- The tissues pierced are (in order): skin, subcutaneous tissue, supraspinal ligament, interspinal ligament, ligamentum flavum, dura mater, the arachnoid mater and into the subarachnoid space.

- if instead CSF does not flow. The stylet should be replaced, the needle advanced or withdrawn incrementally, with frequent removal of the stylet Until CSF is obtained or bone encountered.
- When CSF flows
  - ☛ Take adequate sample: If needed 20 up to 30 ml
  - ☛ Observe the appearance: Color/Consistency/Pressure
  - ☛ If contaminated with blood: Wait until CSF clears
- When CSF flows, attach a monometer to obtain pressure if desired. Pressure can only be accurately measured in lateral decubitus position and in relaxed patient
- Attach manometer with a 3-way stopcock when free flow of CSF is obtained
- Read column when highest level is achieved and respiratory variation noted
- The recommended studies include (this order can be changed); collect 1ml of CSF in each of vials
  - ✓ Tube # 1; gram stain, culture and sensitivity
  - ✓ Tube # 2; Glucose and protein
  - ✓ Tube # 3; cell count and differentials
  - ✓ Tube # 4; any special studies you require (fungal/viral/chemical studies)

- Check closing pressure with manometer if desired
- Re insert stylet and remove needle in one quick motion
- Cleanse back and cover puncture site

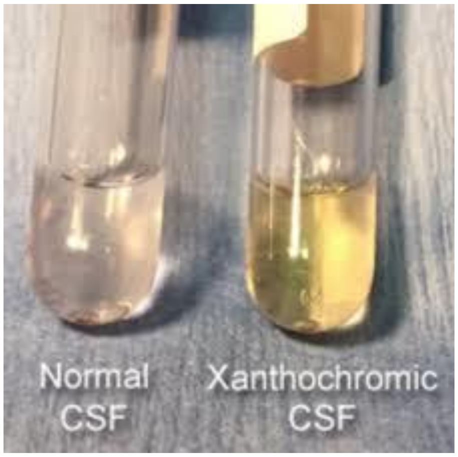
LP - Click on the link below and watch the video

https://youtu.be/YmzDT-LXQPY

2.1.1 CSF analysis

- Opening pressure
  - ✓ Normal value is 70 - 180 mmH2O → see tables below
  - ✓ Measured with manometer
  - ✓ In our set up since we don't have manometer, we use flow rate to estimate opening pressure
    - ☛ Dropping → normal opening pressure
    - ☛ Continues flow (i.e. stream like flow) → increased opening pressure which may suggest increased ICP and give special attention for this patient.
- Appearance and CSF pressure
  - ☛ Turbidity
    - ✓ Crystal clear → normal
    - ✓ Cloudy → bacterial, TB, fungal
    - ✓ Clear → viral
  - ☛ Color → normal CSF has crystal color
    - ✓ Bloody (hemorrhagic) → SAH (usually xanthochromic), traumatic
    - ✓ If CSF is bloody, how do you differentiate traumatic CSF from SAH

Traumatic CSF	SAH
Blood stopes with in short period of time and you may see clear CSF Blood in CSF clots after centrifugation Bright red blood	Continuous blood comes throughout the procedure Blood in CSF doesn't clot after centrifugation Xanthochromic in color (due to hemolysis → bilirubin → yellow in color)



  - Viscosity
- Microscopic and Microbiologic tests
  - Cell count with differential
  - CSF organisms (gram stain)
    - ✓ CSF gram stain has 60-90% sensitivity
  - CSF Cytology
  - CSF culture → has 70-80% sensitivity
- Chemical analysis
  - Glucose
  - Protein
  - Lactate and LDH
  - PH
  - Glutamine and acid-base tests
- Specific tests

N.B **CSF analysis in our set up**

- In our set up, we usually collect 2-3 ml of CSF with one bottle (rather than using 4 bottles as a standard) and we request with different request papers like below
  - ✓ Request # 1; cell count with differentials
  - ✓ Request # 2; Gram stain and AFB
  - ✓ Request # 3; Glucose and protein
  - ✓ Request # 4; culture
- You may keep the sample for other available investigations based on indication like
  - ✓ Gene expert → TB meningitis
  - ✓ Cytology → carcinomatous meningitis
  - ✓ Indian ink → cryptococcal meningitis especially in RVI Pt

N.B Rule of 2 → has > 98% specificity for bacterial meningitis

➔ CSF WBC > 2,000

- ➔ Glucose < 20
- ➔ Total protein > 200

Table 1: CSF findings in different forms of meningitis

	Appearance	*Opening Pressure (mmH_2O)*	*Cell count or WBC count (per μL) with dominant differential count* *	*Glucose (mg/dL)*	*Protein (mg/dL)*	*Microbiology*
Normal	clear	70-180	0-5; lymphocytes	50-75	15 — 45	***No organisms***
Aseptic meningitis		90-200	10-300; lymphocytes	Normal	Normal, may be Slightly ↑	*Negative finding on workup*
Viral meningitis						*Viral isolation, PCR*
Bacterial meningitis	cloudy	200-300	100-5000; >80% PMNs	< 40 (low)	High (> 100)	**Gram stains** +ve in > 60% & **Culture** +ve in > 80%
Tuberculous meningitis		180-300	100- 1000; lymphocytes, sometimes with a predominance of neutrophils in the early stage	< 40 (low)	High (> 100 /100 - 800/)	**AFBs** are infrequently seen (+ve in upto 40% of cases) on direct smear of CSF sediment **Culture** +ve in 50 - 80%, gold standard **Gene X-pert, has** sensitivity of up to 80% and is the preferred initial diagnostic option
Cryptococcal meningitis		180-300	10-200; lymphocytes	Reduced	High (50-200)	***India ink*** (+ve 60-80%*)*, ***cryptococcal antigen*** (> 95 % sensitive and specificity*)*, ***culture*** (+ve 95-100%)

* **Cell count** values are variable from reference to reference. So*, **for clinical practice differentiate either neutrophil dominance (bacterial meningitis) or lymphocyte dominance (other than bacterial meningitis), cell count in thousands (bacterial meningitis) or in hundreds (other than bacterial meningitis).***

Table 2; normal CSF composition

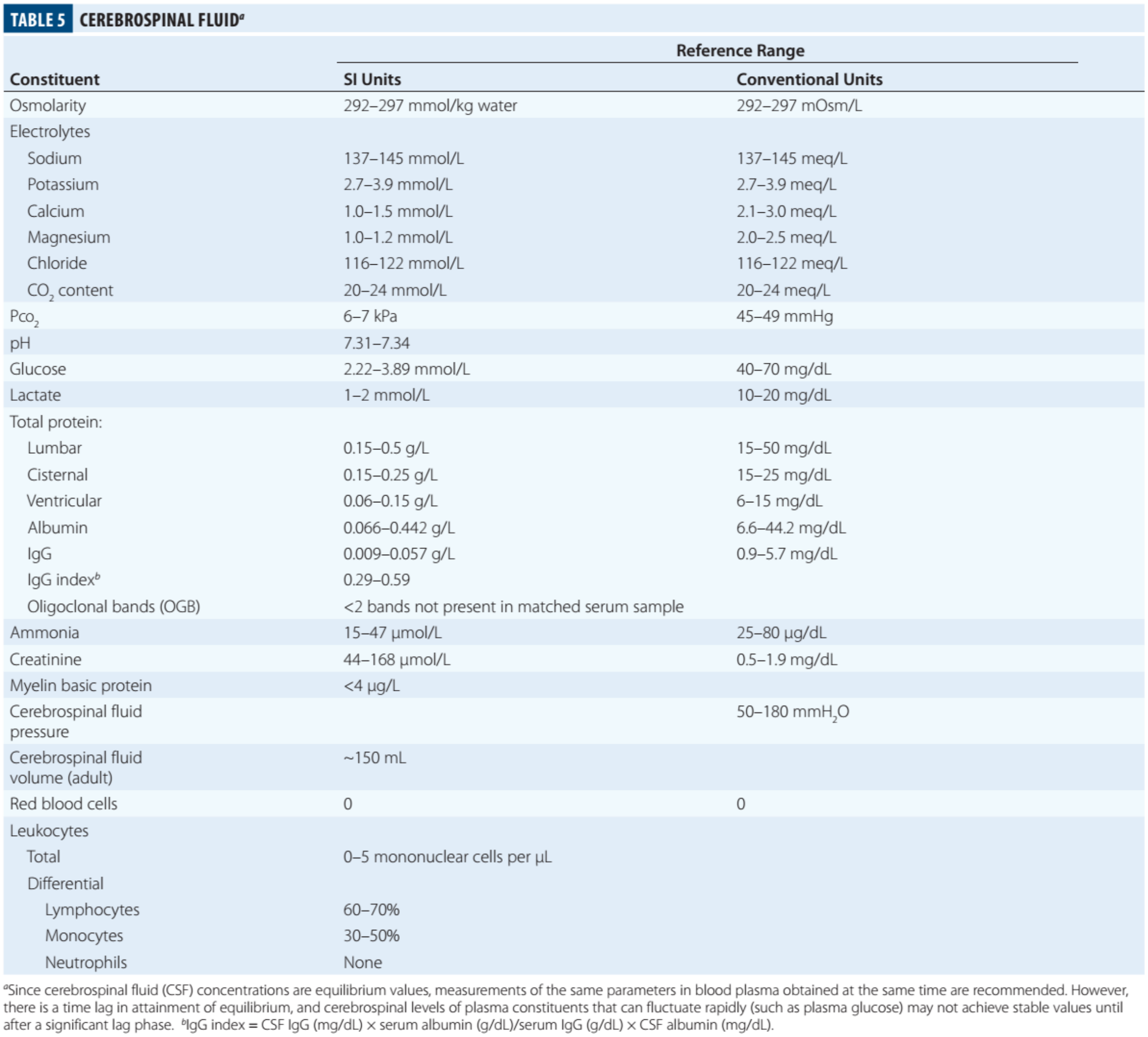


TABLE 5 CEREBROSPINAL FLUID[a]

Constituent	Reference Range	
	SI Units	Conventional Units
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO_2 content	20–24 mmol/L	20–24 meq/L
Pco_2	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein:		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
Creatinine	44–168 µmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 µg/L	
Cerebrospinal fluid pressure		50–180 mmH_2O
Cerebrospinal fluid volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per µL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a] Since cerebrospinal fluid (CSF) concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase. [b] IgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

Composition of the Cerebrospinal Fluid

- **CSF resembles water**; the protein content is low
- **No more than 5 lymphocytes** and **a neutrophil** are present.
- **Glucose** values are **2/3rd** of those in **blood.**
- CSF **glucose** concentrations <2.2 mmol/L **(<40 mg/dL) are abnormal**,
- And a CSF **glucose** concentration of **zero** can be seen in **bacterial meningitis.**
- Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration.
- The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6.
- A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis.
- It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; Therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, Is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.
- Some IgG is produced in the brain and proteins are scarce
- Higher levels of sodium, chloride, and magnesium and PCO2
- Lower levels of potassium, calcium, bicarbonate and PH

2.2 Pleural tap (thoracentesis)

Indications	Contra indications	CXN
Diagnostic ✚ **newly detected pleural effusion** ☛ to determine the nature of the effusion (ie, transudate, exudate) and to identify potential causes ☛ A unilateral effusion, especially if it is left-sided ☛ Bilateral effusions that are of disparate sizes ✚ Atypical features that should prompt consideration of diagnostic thoracentesis in a patient with suspected HF ☛ alternate etiology of the effusion (eg, bilateral effusions of significantly disparate sizes (especially if the effusion on the left is larger than on the right) ☛ symptoms of pleurisy ☛ fever ☛ features suggestive of infection or cancer ☛ an echocardiogram that is inconsistent with HF ☛ a disproportionately high alveolar-arterial oxygen gradient, and/or the lack of resolution with effective HF therapy. ☛ Normal cardiac silhouette on chest radiograph ☛ An echocardiogram that is inconsistent with heart failure **Therapeutic** ✚ symptom relief (eg, dyspnea) ✚ if the fluid has imaging characteristics of a complicated pleural effusion (eg, loculations suggesting a parapneumonic pleural effusion) ✚ pleural conditions that risk pleural thickening and restrictive functional impairment, such as effusions due to post-primary or reactivation tuberculosis and hemothorax. ✚ Therapeutic removal of small pneumothorax.	✚ Anticoagulation or a bleeding diathesis: ✓ with a PT or PTT > 2x midpoint of the normal range (INR >2), ✓ a platelet count < 50,000 /mm3, ✓ a serum Cr > 6 mg/dL ✚ insufficient pleural fluid ✓ <1 cm distance from the pleural fluid line to the chest wall on a decubitus chest radiograph ✚ Mechanical ventilation: ✓ bronchopleural fistula, if a pneumothorax does occur ✚ Active skin infection at the point of needle insertion NB: - *There is no absolute contraindication for thoracentesis*	✚ Pain at the puncture site ✚ Bleeding (e.g. bleeding from intercostal vessel creating subcutaneous hematoma, haemothorax, or hemoperitoneum) ✚ Pneumothorax ✚ Infection (empyema, soft tissue infection) ✚ Laceration of lung. ✚ Spleen or liver puncture (don't go below 9th ICS) ✚ Vasovagal events ✚ Seeding the needle tract with tumour ✚ Re-expansion pulmonary oedema (caused by withdrawal of > 1000ml fluid at once)

Equipment's

- ✓ Sterile gloves, mask, and gown.
- ✓ Iodinated skin preparation with sterile sponges.
- ✓ Sterile towels.
- ✓ Local anaesthetic (1% lidocaine without epinephrine).
- ✓ 5-mL syringe with 25-gauge needle.
- ✓ 18-gauge 2-inch needle.
- ✓ Collection basin.
- ✓ 3-way stopcock.
- ✓ 20-60ml syringe.
- ✓ *For therapeutic tap, in our setup, we were using IV set with needle tip and locally available Highland/or empty RL bag as a container for fluid collection*

Patient preparation

- Patient should have intravenous access.
- Oxygen should be available.
- Monitor oxygen saturation with pulse oximetry.
- Younger patients may need sedation for procedure.
- Explain procedure before and during procedure.

Patient positioning

- Pleural effusion.
    - Sitting upright with arms supported on table in front of patient
    - Lying in lateral decubitus position with effusion side down.
- Pneumothorax: Supine with head of bed up 30 degrees.

procedures

Locate Effusion

- ✓ Chest radiograph.
- ✓ Manual percussion to find onset of dullness.
    - One to two interspaces below the level at which breath sounds decrease or disappear on auscultation, percussion becomes dull, and fremitus disappears.
    - Above the ninth rib, to avoid subdiaphragmatic puncture.
    - Midway between the spine and the posterior axillary line, because the ribs are easily palpated in this location.
- ✓ Effusion is usually accessible via the sixth or seventh intercostal space just distal to the scapular tip in the mid scapular line or posterior axillary line
- ✓ If pneumothorax is present, it is usually accessible via the second intercostal space anterior

Ultra-sonogram marked location.

- ✓ Mark location of effusion with the patient in the same position as necessary for procedure.
- ✓ If possible, do not move patient after marking the location because the fluid may shift.
- Use a 25-gauge needle and 5-ml syringe to infiltrate the skin and make a wheal under the skin.
- Change needle to 18 gauge with 2-inch needle.
- Going over top of sixth rib, infiltrate through wheal, over top of rib to anesthetize the periosteum, and into pleural space.
- Be sure to aspirate first, and know when you are in the pleural space.
- The parietal pleura needs to be anesthetized. but, to avoid a puncture of the lung, do not advance the needle further.
- When in the pleural space, a ‘pop’ may be felt and fluid or air will enter syringe.

Removal of Pleural Effusion for Diagnostic Evaluation

- Remove lidocaine syringe and needle to outside the pleural space, with needle still inserted but outside the pleural space; replace syringe with empty 20-60 ml syringe.
- Reinsert needle into pleural space while applying gentle negative pressure on syringe.
- When in pleural space, a ‘pop’ may be felt and fluid or air will enter syringe.
- Remove effusion into syringe.
- Remove needle and apply bandage to area.

Thoracentesis - Click on the link below and watch the video

https://youtu.be/UBY3cQiQ6Ko

2.2.1 pleural fluid analysis

1. Gross appearance
    - Pale yellow (Straw) → **transudative** effusion, some exudates
    - Milky → **chylothorax** (thrombus in left subclavian vein, malignancy, trauma, TB)
    - Bloody → **haemothorax** (malignancy, trauma, TB, pulmonary infarction), **traumatic procedure**
    - Frank pus → **empyema** (TB, pulmonary infection, trauma, oesophageal rupture)
    - Turbid → **inflammatory exudate**

2. **Cell count with differentials**
3. **Gram stain and AFB**
    - **AFB +ve in 10 - 25% of TB pt's**
4. **Glucose and protein**
5. **Culture**
    - **+ve in 25 - 75% of TB pt's**
6. **Gene x-pert** (X-pert MTB/RIF)
    - **75% +ve**

routinely done in our set up

7. Others
    - PH
    - Cytology → **sensitivity of approximately 60 %** for the diagnosis of malignant effusion (sensitivity in lung cancer; 78 % for adenocarcinoma, 53 % for small cell carcinoma, and 25 % for squamous cell carcinomas)
    - LDH
    - Amylase → increase in acute/chronic pancreatitis (one cause of exudative effusion)
    - ADA (Adenosine deaminase)
        - may be helpful to **distinguish between malignant and tuberculous pleurisy** when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative
        - > 35 to 50 U/L in tuberculous pleural effusions (The most common diagnostic threshold used to establish **tuberculous pleural effusions is a value >40 U/L**)
        - **< 40 U/L in 94 % of malignant pleural effusions**.

N.B

- Pleural tap should be done
  - over the area of dullness
  - above the rib to avoid neurovascular injury
- don’t go below 9th ICS to avoid visceral injury
- estimated volume of fluid to be drawn
  - for culture → 20 ml
  - for cytology → 20 ml
  - for biochemical and microbiology (protein, glucose, cell count, gram stain and AFB, LDH, PH) → 10 ml

Lights Criteria		
Characteristics	**Transudative**	**Exudative**
1. Pleural fluid **protein** / serum protein ratio	< 0.5	> 0.5
2. Pleural fluid **LDH** / serum LDH ratio	< 0.6	> 0.6
3. Pleural fluid LDH	< 2/3rd the upper limit of the normal laboratory serum LDH level	> 2/3rd the upper limit of the normal laboratory serum LDH level
At least One of the three criteria should qualify to diagnose exudative effusion		

other Criteria		
Criteria	**Transudative**	**Exudative**
1. Cell count	< 100 x10^6 / L	> 500 x10^6 / L
2. Differential cell	Lymphocyte	Different
3. Pleural fluid LDH	< 0.45 times the upper normal limit serum LDH	> 0.45 times the upper normal limit serum LDH
4. LDH	< 200 IU/ L	> 200 IU / L
5. Pleural fluid cholesterol	< 45 mg/dL	> 45 mg/dL
6. Pleural fluid protein	< 3 g/dL (<30g/L)	> 3 g/dL (>30g/L)
7. Cause	non-inflammatory	inflammatory, tumour
8. Appearance	light yellow	yellow, purulent
9. pleural fluid pH	7.40 to 7.55	7.30 to 7.45
10. Specific gravity	<1.018	>1.018
NB: - CHF patients with acute diuresis can have pleural fluid protein > 3g/dl; However, such patients have a pleural fluid to serum albumin gradient > 1.2 g/Dl		

DDX for some abnormal pleural fluid analysis findings

- LDH > 1000 IU/L
  - Empyema
  - Malignancy
  - Rheumatoid disorders (SLE, RA)

- **Glucose**

  Glucose < 30 mg/dl
    - Empyema
    - Rheumatoid disorders

  Glucose between 30 - 50 mg/dl
    - SLE
    - Malignancy
    - TB
- **Lymphocytes**

  Lymphocytes 85% - 95 %
    - **TB**
    - **Lymphoma**
    - Chylothorax
    - Sarcoidosis
    - Rheumatoid disorders

  Lymphocytes between 50 - 70%
    - Malignancy
- **Eosinophilia** — defined by pleural fluid eosinophils representing >10 % of the total nucleated cells
    - Pneumothorax, Hemothorax, Pulmonary infarction
    - **Parasitic disease**
    - **Fungal infection** (coccidioidomycosis, cryptococcosis, histoplasmosis)
    - **Malignancy (carcinoma, lymphoma, myeloma)**
    - **Tuberculous pleurisy**
    - **Parapneumonic effusions**
    - **Chronic eosinophilic pneumonia**
    - Drugs
    - Benign asbestos pleural effusion
- Mesothelial cells
    - prominent in transudative pleural effusions, and are variable in exudative effusions.
    - in exudative effusion; **tuberculosis is unlikely if there are > 5% mesothelial cells**
- ADA
    - > 35 - 50 U/L (especially when lymphocytes > 75%) Supports TB
    - < 40 U/L, suggests malignancy, rarely caused by TB
- **Amylase:** pleural/serum Amylase ratio > 1.0
    - Acute/chronic pancreatitis
    - Oesophageal rupture
    - Malignancy

2.3 Peritoneal tap (paracentesis)

Indications	Contra indications	CXN
Diagnostic sampling of ascitic fluid ✓ e.g. **identification of infectious organism in spontaneous**	**Absolute:** - ▪ Unstable airway. ▪ Hemodynamically unstable patient.	Pneumoperitoneum. Perforation: Intestine, organ. Bleeding. Infection.

bacterial peritonitis. internal bleeding following blunt abdominal trauma, chylous ascites after surgery, rule out malignancy, ✚ Therapeutic removal of the huge ascitic fluid	▪ Intestinal perforation. **Relative: -** ▪ Infection of the abdominal wall. ▪ Coagulopathy (prothrombin time > 18 seconds). ▪ Thrombocytopenia (platelet count <100,000/µl). ▪ Recent intestinal tract surgery (< 1 month ago).	✚ Leakage of ascitic fluid ✚ Hypoproteinaemia if repeated tapping done

Equipment

- Alcohol swabs, povidone-iodine.
- 23-gauge and 21-gauge needles or angiocatheters with syringes.
- Local anesthetic (e.g. 1% lidocaine).
- Large bore needle with plastic catheter.
- Sterile containers for fluid collection.
- Appropriate culture tubes for microorganisms.
- *For therapeutic tap, in our setup, we were using IV set with needle tip and locally available Highland/or empty RL bag as a container for fluid collection*

Patient preparation and position

- ✓ Explain indication and risks to the patient.
- ✓ Inform the patient of the intention of the procedure.
- ✓ Supine or side.

Procedure

- The puncture site should be shaved, if necessary, and cleansed with povidone-iodine.
- Inject local anaesthetic, infiltrating the skin first and then penetrating into deeper layers.
- A small 3-mm incision can be made with a scalpel to help insert the needle. Using **Z-track technique** *(to prevent fluid leakage),* insert the tap needle 1-2 inches into the abdomen
- Obtain a sample of fluid or withdraw as much fluid as necessary with a syringe (in case of therapeutic lavage)
- Remove the needle and apply a pressure dressing to the puncture site.
- If an incision was made, it may be closed using 1 or 2 stitches.
- The ascitic fluid removed may be replaced 1:1 with 5% albumin IV.

Paracentesis - Click on the link below and watch the video

https://youtu.be/0bvMt-A6VhQ

2.3.1 Ascitic fluid analysis

a) Inspection of gross appearance
- ☛ Straw coloured → cirrhosis, budd chiarry sxx, CHF, constrictive pericarditis, meig's sxx
- ☛ Chylous (milky) → lymphatic obstruction
- ☛ Haemorrhagic (bloody) malignancy, abdominal trauma, TB, acute pancreatitis
- ☛ Cloudy → TB

b) **Cell count**
- ✓ Normal → WBC < 500/ml, neutrophil < 250/ml
- ✓ Neutrophil dominant → bacterial peritonitis

Bacterial peritonitis	
SBP	Secondary peritonitis due to rupture of abdominal viscus
✓ **WBC > 500/mm3 (neutrophil ≥ 50%)** ✓ **Mono microbial**	✓ **WBC > 10,000/mm3 (significant leucocytosis)** ✓ **Multiple organisms identified** ✓ Increased LDH level ✓ Glucose < 50 ✓ Protein significantly decreased ✓ PH ✓ With obvious cause of 2ry peritonitis like intestinal perforation ✓ Failure to improve after standard treatment with in 48 hr's

- ✓ Lymphocyte dominant
    - ☛ TB peritonitis
    - ☛ Abdominal carcinomatosis

c) **Glucose and protein**

d) **Gram stain and AFB**

e) **Culture** → inoculation at bedside increase sensitivity to 85% to identify infection

f) **SAAG (serum ascitic albumin gradient)**
- ☛ SAAG = serum albumin level - ascitic albumin level
- ☛ **SAAG > 1.1 g/dl** → Cause of ascites is most likely **Portal HTN** (e.g. cirrhosis, chronic hepatic congestion from CHF)
- ☛ **SAAG < 1.1 g/dl** → Non-Portal HTN (e.g. TB peritonitis, Nephrotic sxx, peritoneal carcinomatosis, hypalbuminemia)
- ☛ 95% accurate but can't r/o malignancy
- ☛ Ascitic fluid protein < 1g/dl predispose to SBP

g) Other
- ✓ RBC → > 50,000 RBC/μl suggest haemorrhagic ascites
- ✓ PH → PH < 7 suggest bacterial infection
- ✓ Cytology → for malignancy
- ✓ Amylase → increased level in ascites 2ry to chronic pancreatitis

N.B Ascitic fluid analysis in our set up

- In our set up, we usually collect ascitic fluid with one bottle and we request with different request papers like below
    - ✓ Request # 1; cell count with differentials

- ✓ Request # 2; Gram stain and AFB
- ✓ Request # 3; Glucose and protein
- ✓ Request # 4; culture

- If you suspect peritoneal carcinomatosis, you have to request cytology from ascitic fluid

2.4 BM aspiration

Indications	Contra indications	CXN
- VL - Diagnosis and staging of hematologic disease - Myeloproliferative disease - Unexplained Pancytopenia - assessment of overall bone marrow cellularity. - Bone marrow failure (including acquired aplastic anemia, Fanconi anemia, Diamond- Blackfan syndrome). - Fever of unknown origin. - Storage disease. - Monitoring during chemotherapy or following stem cell transplantation (aspiration only).	**Absolute** - Osteomyelitis - Infection at the site of puncture **Relative** - Congenital factor deficiency or acquired coagulation defect. - Anticoagulation with warfarin or heparin. - Severe thrombocytopenia - Infection or prior radiation at sample site.	- Bleeding at any site, with or without development of a hematoma ✓ rare if adequate pressure is applied. ✓ Bleeding risk has been reported to be increased in those with osteoporosis or extensive bony involvement by disease, such as multiple myeloma. - Retroperitoneal haemorrhage - Osteomyelitis - needle breakage - Infection (rare) - Bone pain

Equipment

Site Preparation

- ❖ 10% povidone-iodine.
- ❖ Alcohol preparation pads or swabs.
- ❖ Sterile gloves, gown, and drape
- ❖ Spinal and subcutaneous needles, 20 to 26 gauge.
- ❖ 1% lidocaine hydrochloride, injection.
- ❖ 8.4% sodium bicarbonate, injection, USP

Marrow Aspiration

- ✓ Bone marrow aspiration needles

Biopsy aspiration needles	**recommended sizes**
Regular/Adults	4-inch, 11-gauge
Adults:	4-inch, 8-gauge
Orthopedic:	6-inch, 10/11-gauge
Pediatric:	3½-inch, 13-gauge
Infant:	2-inch, 13-gauge

- ✓ Sterile syringes, 10 to 20 mL
- ✓ clean microscope slides

- ✓ wooden applicator or tooth picks
- ✓ spirit lamp with sufficient flame
- ✓ sterile cotton and gauze
- ✓ plaster, labels, pen and pencil/marker
- ✓ Container with fixative for trephine biopsy specimen.
- ✓ Vacutainers; one for sodium heparin and one for EDTA (ethylene diamine tetra acetic acid).
- ✓ Bandages.

Choice of site

- Posterior superior iliac spine
- Anterior iliac crest in obese patients
- 1st part of body of manubrium of sternum

Procedure

- Place the patient in a right or left lateral decubitus position with the back comfortably
  flexed and the top knee drawn toward the chest.
- Locate the posterior iliac spine and mark it with ink or thumb nail pressure.
- Using sterile technique, prepare the skin with anti-septics and drape.
- Using a sterile syringe, infiltrate the marked area with local anesthesia especially the periosteum.
- Make a 3-mm skin incision with a scalpel blade over the marked area
- Hold the needle with the proximal end between the palm and the index finger against the shaft near the tip.
- With the stylet locked in place, introduce the needle through the incision pointing toward the anterior superior iliac spine and bring it into contact with the posterior iliac spine.
- Using gentle but firm pressure, advance the needle to bore through the iliac spine.
- Rotate the needle in an alternating clock-wise and counter-clockwise motion. Entrance into the marrow cavity is generally detected by decreased resistance.
- Remove the stylet, and check for marrow material. If not present, proceed to bore until marrow is found in the tips of the stylet.
- With a syringe locked into the proximal portion, apply a negative pressure.
- This first pull contains the marrow particles or spicules that should be used for preparing initial smears.
- A heparinized, larger syringe (30 mL) may be used to obtain additional marrow for cytogenetic analysis, flow cytometry, and other studies.

Bone marrow aspiration - Click on the link below and watch the video

https://youtu.be/svTQ-zJHY9M

2.5 Splenic Aspiration

Indications	Contra indications	CXN
✚ VL ✚ Haematologic malignancy	✚ **Massive splenomegaly** ✚ **Small spleen** → led to bleeding to the extent of splenectomy ✚ **Thrombocytopenia** (platelet count < 40,000/ml) ✚ **Massive ascites** ✚ **Overlying skin infection** ✚ **severe anemia** (hemoglobin ≤ 5 g/l) ✚ difference in prothrombin time between patient and control > 5 s ✚ **signs of active bleeding** (e.g. epistaxis, rectal bleeding, skin bruises) ✚ jaundice (a potential marker of liver dysfunction) ✚ pregnancy → spleen barely palpable ✚ bad general condition (e.g. cardiovascular shock, altered consciousness)	✚ Bleeding ✚ Splenic rupture to the extent of death

Prerequisite

- ❖ The two important prerequisites for the safety of the procedure are;
  - **Rapidity** so that the needle remains within the spleen for less than l second and
  - **precision** so that the entry and exit axes of the aspirating needle are identical to avoid tearing the splenic capsule.
- ❖ splenic aspiration **should be performed in a hospital setting** where blood transfusion is possible because the procedure is associated with a risk of fatal internal bleeding.
- ❖ This procedure also **requires considerable technical expertise** for making the aspiration and facilities for **nursing surveillance, blood transfusion, and surgery**.

Procedure

i. Clean three glass slides and label them. If culture medium is required, label in the same way as the slides. Attach a 11/4-inch × 21-gauge (32 × 0.8-mm) needle to a 5ml syringe.

ii. Inform the patient about the procedure. Check all clinical and biological contraindications again. Palpate the spleen and outline its margins on the patient's abdomen with a pen. For safety, the spleen should be palpable at least 3 cm below the costal margin on expiration. Use an alcohol swab to clean the skin at the site of aspiration and allow the skin to dry.

iii. With the 21-gauge (0.8 mm) needle attached to the 5ml syringe, just penetrate the skin, midway between the edges of the spleen, 2—4cm below the costal margin. Aim the needle cranially at an angle of 45° to the abdominal wall. The actual aspiration is done as follows:

- ❖ pull the syringe plunger back to approximately the 1ml mark to apply suction and with a quick in-and-out movement push the needle into the spleen to the full needle depth and then withdraw it completely, maintain suction throughout.

iv. For young, restless children, have two assistants hold the child (arms folded across the chest, with shirt raised to obstruct the line of vision, and pelvis held firmly). Carry out the aspiration as a single-stage procedure using the same landmarks, angles and suction as in

step 3 — all in one quick motion. The insertion should be timed with the patient's breathing so that the diaphragm is not moving. This should be done during fixed expiration if the child is crying. Only a minute amount of splenic material is obtained for culture and smear.

v. If culture is available: *slowly pull* the plunger back to the 2—3ml mark and, by using sterile techniques, insert the needle into a tube containing culture medium and *briskly push* the plunger into the barrel to expel the contents of the needle onto the side walls of the tube. If necessary, repeat once or twice until splenic material is visible in the tube. Replace the cap on the tube and invert to wash splenic material on the side of the tube. Repeat the procedure for the second tube of culture medium. Sterile techniques are essential throughout.

vi. Expel material gently onto glass slides, holding the needle tip on the surface of the slide. Immediately spread evenly with the needle, using a linear (not circular) motion. The smear should be slightly thinner than a thick blood film for malaria. Remove the needle and use the end of it to obtain additional material from the tip of the syringe and spread it on slides. Further material found on the end of the plunger may be dabbed directly onto a slide and spread. Allow the slides to dry.

vii. Write the time of aspiration on the patient ‘s chart with the instructions: “Record pulse and blood pressure every half hour for 4 hours, then every hour for 6 hours. Patient must remain in bed for 12 hours!” Ensure that the patient understands the instructions. Enter the procedure in the notes and sign.

viii. Take the slides (and medium) to the laboratory for preparation and microscopic examination.

Splenic aspiration - Click on the link below and watch the video

https://youtu.be/6egWxe4VFT4

2.6 LN aspiration

Indications	Contra indications	CXN
✚ TB lymphadenitis ✚ VL ✚ Lymphoma ✚ Sentinel LN of any malignancy	✚	✚

Materials required:

- Sterile needle (21G)
- Syringe (10ml)
- Clean glass slide
- Iodine (disinfectant) or sterile cotton swabs
- Cotton wool

Procedure

- Allow the patient to lie comfortably. Prepare the syringe by pulling the piston back as far as possible.
- Feel and locate a swollen gland.

- Disinfect the chosen site with swollen glands using a piece of cotton wool soaked in iodine or another suitable disinfectant.
- Take the gland between the thumb and index finger of the left hand. Hold it steady and make it at the same time standing out.
- Introduce the needle with a right angle into the center of the gland in two stages:
  - First pierce the skin
  - Second penetrate the gland
- With your left hand, gently knead the gland. With your right hand, revolve the needle in both directions. The glandular fluid will ooze into the needle.
- Withdraw the needle in one rapid movement while holding the thumb over the hub. Then apply a swab dipped in iodine to the point of entry.
- Attach the syringe (piston pulled back) to the needle. Place the needle on the slide. Push the piston gently down the barrel to discharge the glandular fluid contained in the needle onto the slide.
- Make a thin film using the fluid on the slide. The fluid can be discharged in more than one slide.

Chapter 3; Emergency and OPD Cases/Viva/

Dr. Mulualem. G

3.1 Shock

- Shock is the clinical condition of **organ dysfunction resulting from an imbalance between cellular oxygen supply and demand.**
- There are a multitude of heterogeneous disease processes that can lead to shock.
- **The organ dysfunction** seen in early shock **is reversible** with restoration of adequate oxygen supply.
- **Left untreated**, shock transitions from this reversible phase to an irreversible phase and death from **multisystem organ dysfunction (MSOF).**

Classification of shock

- While there is a heterogeneous list of specific conditions that can cause shock, it can be classified into four major shock types based on the primary physiologic derangement leading to reduced oxygen delivery and cellular hypoxia.
- The four major shock types are
    - Distributive
    - Cardiogenic
    - Hypovolemic, and
    - Obstructive

Major shock types and specific disease processes that can result in that physiologic derangement.

Hypovolemic shock

- Hemorrhagic shock
- Non hemorrhagic
    - GI losses
    - Burns
    - Polyuria
        - DKA
        - Diabetes insipidus

Cardiogenic shock

- Myocardial infarction
- Myocarditis
- Arrhythmia
- Valvular
    - Severe aortic valve insufficiency
    - Severe mitral valve insufficiency

Obstructive shock

- ❖ Tension pneumothorax
- ❖ Cardiac tamponade
- ❖ Restrictive pericarditis
- ❖ Pulmonary embolism
- ❖ Aortic dissection

Distributive shock

- ❖ septic shock.
- ❖ Anaphylactic shock
- ❖ neurogenic shock
- ❖ Pancreatitis
- ❖ Severe burns
- ❖ Endocrine shock
- ❖ Adrenal crisis

Table; Hemodynamic Characteristics of the Major Types of Shock

Type	**Hemodynamic change**			
	Preload	**Afterload**	**SVR (systemic vascular resistance)**	**CO (Cardiac output)**
Hypovolemic	Decreased	Increased	Increased	Low
Cardiogenic	Increased			
Obstructive	Decreased			
Distributive	Decreased		Decreased	High

Mixed Shock

- The types of shock outlined in this classification scheme are not mutually exclusive; not uncommonly, **a patient will present with more than one type of shock.**
- The initial physiologic disturbance leading to reduced perfusion and cellular hypoxia in sepsis is distributive shock. In this setting, **a sepsis-induced cardiomyopathy** can develop, which reduces myocardial contractility, thus producing a cardiogenic component to what now would be described as a mixed type of shock.

Undifferentiated Shock

- **Upon initial presentation**, many patients have undifferentiated shock in which the shock type and specific disease process are not apparent.
- The type of shock seen most commonly is dependent upon the clinical area of practice.
  - In the medical ICU, the largest number of patients have distributive shock related to sepsis.
  - A cardiac ICU will have a population weighted toward cardiogenic or obstructive types of shock.
  - The emergency department will see more of a mix of patients with

trauma patients presenting with hypovolemic shock and septic patients having a distributive pathophysiology.

Stages of shock

- Regardless of type, shock progresses through a continuum of **three stages**. These stages are;
    - **Compensated shock (pre-shock)**
    - **Shock (decompensated shock), and**
    - **Irreversible shock.**
- Compensated shock
    - The body utilizes a variety of physiologic responses to counteract the initial insult and attempts to reestablish the adequate perfusion and oxygen delivery.
    - At this point, there are no overt signs of organ dysfunction.
    - Laboratory evaluation may demonstrate mild organ dysfunction (i.e., elevated creatinine or troponin) or a mild elevation of lactate.
    - The specific compensatory response is determined by the initial pathophysiologic defect.
    - In early sepsis with reduction in SVR, there is a compensatory rise in HR (and CO).
    - With early hemorrhagic volume loss, there will be a compensatory increase in SVR.
- Shock (decompensated shock)
    - As the host compensatory responses are overwhelmed, the patient transitions into true shock with evidence organ dysfunction.
    - Appropriate interventions to restore perfusion and oxygen delivery during these initial two phases of shock can reverse the organ dysfunction.
- Irreversible shock
    - If untreated the patient will progress to the third phase of irreversible shock.
    - At this point, the organ dysfunction is permanent and often the patient progresses to MSOF (multisystem organ failure).

Approach to shock patient

- **This early recognition of the presence of shock is an essential tenet of shock care.**
- A second aim of the initial assessment (history, physical examination, and diagnostic testing) is to identify either a specific shock etiology or to determine the type of shock present.

Clinical feature of shock in general

- WHO criteria for shock
    - ✓ SBP< 90mmhg

- ✓ Cold extremities
- ✓ Fast and weak pulse, or absent pulse
- ✓ Prolonged capillary refill time **> 3 seconds** *(clinically 3 second is approximated with counting ''1001, 1002, 1003 = 3sec'')*

History

- Obtaining a **concise, focused history** is essential.
- If the patient is unable to provide a history, ancillary information from anyone accompanying the patient should be obtained, and a brief chart review should be performed.
- As the history is being obtained, the clinician must be attentive to any details indicating new organ dysfunction.

  - a newly **altered mental status** or decrease in renal function (**oliguria**).
  - Patients with **distributive shock from sepsis** may present with **fever and a history revealing of a focal site of infection**.
  - **Anaphylactic distributive shock** may be suggested by the onset of **hives, dyspnea, and new facial edema after exposure to common allergens**.
  - **Cardiogenic shock** may be identified by the onset of **exertional chest discomfort**.
    - ✓ The patient with **significant arrhythmia** may have an initial complaint of **palpitations with syncope or presyncope**.
  - **Hypovolemic shock** may be identified in patients who present with a history of **trauma** (blunt or penetrating) or **GI bleed** (hematemesis, melena, or bright red blood per rectum).
  - **Obstructive shock**
    - ✓ A patient with **hypertension** and **tearing chest or back pain** may be presenting with acute aortic dissection and **obstructive type shock**.
    - ✓ **Acute onset chest pain with dyspnea** in the setting of immobility and or underlying malignancy raises concern for obstructive shock due to **pulmonary embolism.**
  - **For most patients, the specific etiology will be less clear** but the history can be helpful in raising the likelihood of a particular type of shock.
    - ✓ As an example, a patient with a preexisting immune dysfunction or medication-induced neutropenia may present with hypoperfusion and new organ dysfunction, in which the clinician must have a high suspicion for septic shock.
    - ✓ Similarly, a patient with extensive cardiac disease requires a higher suspicion for cardiogenic shock.

Physical Examination

- The physical examination should be conducted with the **aim of answering two**

questions.

- **Is shock present** (either in compensated stage prior to overt evidence of organ dysfunction or decompensated indicated by the presence of new organ dysfunction)?
- Secondly, **what type of shock is present** (distributive, cardiogenic, hypovolemic, or obstructive)?

- The physical examination findings present during the **compensated phase of shock tend to be nonspecific**. These include;
  - **Tachycardia** → with the body's attempt to increase CO
    - Fast and weak pulse, or in severe cases, absent pulse
  - **Tachypnea** → to compensate for the developing metabolic acidosis.
- Hypotension (MAP of <60 mmHg or SBP < 90 mmHg)
  - but this finding is not always present.
  - Many patients may have underlying conditions that cause longstanding low blood pressure without any evidence of organ dysfunction.
  - Alternatively, patients with underlying hypertension may develop organ dysfunction at higher blood pressures.
- The CNS, kidney, and skin examination are "windows" through which we can identify organ dysfunction.
  - Confusion and encephalopathy → due to decreased oxygen delivery to the brain is manifest as
    - In the early stage of shock, the body will redirect blood flow to the CNS to maintain adequate perfusion. In the patient with shock and altered mental status, all the usual compensatory mechanisms have been outstripped by the magnitude of shock pathophysiology.
    - **New encephalopathy represents decompensated shock.**
  - In patients with normal baseline renal function, oliguria (<0.5 mL/kg per h) **may indicate shock**.
    - **a urinary catheter** should be placed for accurate hourly assessment of urine output
  - Finally, decreased capillary refill and cold and clammy skin are signs of hypoperfusion and shock.
- **Raised JVP and peripheral edema** can provide insight into right-sided cardiac pressures overload.
- Pulmonary auscultation can identify signs of left-sided cardiac dysfunction.
- The physical examination may be used to differentiate shock with high CO (distributive) from that with low CO (cardiogenic shock, hypovolemic shock, and obstructive shock).
- **findings suggestive of high output shock** (distributive) include;
  - **warm peripheral extremities**
  - **brisk capillary refill (<2 s), and**
  - **bounding pulses.**
- **Findings suggestive of low CO shock (cardiogenic shock, hypovolemic shock, and obstructive shock) include;**

  - cool extremities
  - delayed poor capillary refill, or
  - weak pulses
- **The JVP may be elevated cardiogenic shock (with right-sided failure) and reduced (JVP <8 cm) in hypovolemic shock.**
- The presence of **cardiogenic shock would be further supported by an S3 gallop**.
- **Notice;** patients with chronic heart failure do not present with the classical findings of acute heart failure. At times, the physical examination may identify the specific etiology of shock. This is particularly helpful in the patient who cannot provide a detailed history.
- Identify the **site of untreated infection** (cellulitis, abscess, infected pressure injury, or focal) as a source of septic shock.
- **a brady- or tachyarrhythmia** may be leading cause to development of shock.
- **large ecchymosis** may indicate a significant bleed related to trauma or spontaneous retroperitoneal bleeding.
- The rectal examination may reveal GI hemorrhage.
- **Pulsus paradox and elevated JVP may suggest the presence of cardiac tamponade.**
- Patients with a **tension pneumothorax** may have;
  - a paucity of breath sounds over the affected side
  - deviation of the trachea away from the affected side, or
  - subcutaneous emphysema.

Shock index (SI) and qSOFA score

- Combinations of easily assessed examination components have been combined to create a scoring system to identify high risk patient populations.
- The shock index (SI) = $\frac{HR(Heart\ rate)}{\text{SBP(systolic blood pressure)}}$
- normal SI = 0.5 - 0.7.
- An elevated SI (>0.9) has been proposed to be a more sensitive indicator of transfusion requirement and of patients with critical bleeding among those with hypovolemic (hemorrhagic) shock than either HR or BP alone.
- The SI may also identify patients at risk for postintubation hypotension.
- This concept of use of a clinical score to identify at-risk patients has been extended to patients with distributive shock from sepsis.
- The **quick Sequential Organ Failure Assessment (qSOFA) score** is a rapid assessment scale that assigns a point for;
  - ✓ SBP <100
  - ✓ RR >22, or
  - ✓ altered mental status (GCS <15).
- **A qSOFA ≥2** (with a concern for infection) is associated with a significantly **greater risk of death or prolonged ICU stay**.

Initial Laboratory Evaluation of Undifferentiated Shock

- CBC (with differential)
  - An elevation of the WBC count may raise suspicion for an infective process, but this is certainly not diagnostic; an accompanying left shift may improve the sensitivity of this measure.
- Urinalysis and urine sediment → to evaluate for pyuria.
- RFT (BUN, creatinine)
- LFT
- PT, PTT, and INR
- Cardiac enzymes → myocardial ischemia, myocarditis, or a pulmonary embolism
- Arterial blood gas
- ECG
  - There may be a bradycardia or tachycardic arrhythmia causing a reduction in CO.
  - ST segment elevation myocardial infarction may be identified.
  - The presence of the S1 Q3 T3 pattern would raise concerns for pulmonary embolism.
  - Reduced voltage in the presence of electrical alternans raises the possibility of pericardial tamponade.
- Echo
  - evaluate LV size, wall thickness, and ventricular function.
  - Ventricular size and thickness can suggest longer standing cardiac processes.
  - Evaluation of LV function through estimation of left ventricular ejection fraction (LVEF), and can identify shock with globally reduced LV function or regional wall motion abnormalities.
  - The assessment of RV function also examines RV size and wall thickness (to identify conditions such as elevated pulmonary pressures or suggest pulmonary embolism), and also evaluate the patient for pericardial tamponade.
  - also be used to assess valve function, including acute processes, such as mitral valve rupture.
- Sepsis workup
  - CBC, U/A
  - Cultures (Blood, urine, stool and sputum cultures)
  - CXR
- Lactate measurement (usually not applicable in our setup)
  - It has a role in the diagnosis, risk stratification, and, potentially, the treatment of shock.
  - Increased lactate (hyperlactemia) and lactic acidosis (hyperlactemia and pH <7.35) are common in shock.
  - Lactate is a product of anaerobic glucose metabolism.

Management of shock

Key Principles in the Treatment of Shock

1. Recognize shock early
2. Assess for type of shock present
3. Initiate therapy simultaneous with the evaluation into the etiology of shock
4. Restoration of oxygen delivery is the aim of therapy
5. Identify etiologies of shock which require additional lifesaving interventions

Management of hypovolemic shock

- Before considering hypovolemic shock rule out cardiogenic shock since the fluid management in cardiogenic shock is challenging with 250ml of NS over 30 min only. If there is misdiagnosis of Cardiogenic shock as hypovolemic shock, iatrogenic fluid overload (like pulmonary edema) will develop during infusion of fluid and worsen the condition.
- If cardiogenic shock is ruled out, search the cause of hypovolemia (is that haemorrhagic or non-haemorrhagic)
- **Infusion of fluid (NS or RL),** 1-2 litres fast for adults and 20 mL/kg for paediatric patients.;
- reassess the patient for adequacy of treatment by Following the BP, PR, UoP & mental status
  - ✓ If responsive, the fluids are slowed to maintenance rates
  - ✓ If not responsive repeat 1x in adult (total 2x) & 2x in paediatrics (total 3x) with maximum tolerated dose being 60 - 80 ml/kg with in the first 1 - 2 hr
  - ✓ If not responsive with the above fluid give blood
  - ✓ If still not responsive consider septic shock
  - ✓ if needed open double IV line.
- If due to hemorrhage, apply transfusion of packed Red Blood Cells (RBC) or whole blood 20ml/kg over 4 hrs, repeat as needed until hemoglobin level reaches 10gm/dl and the vital signs are corrected.
- Better to follow UOP with catheterization

Cardiogenic shock (pump failure)

- Cardiogenic shock (CS) is a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia.
- LV fails to deliver oxygenated blood to peripheral tissues due to variances in contractility, as well as preload and afterload.
- The clinical presentation is typically characterized by persistent hypotension (SBP <90 mmHg unresponsive to volume replacement and is accompanied by clinical features of peripheral hypoperfusion.
- The in-hospital mortality rates range from 40 to 60%, depending on shock severity and the associated underlying cause.
- **Acute MI** with LV dysfunction **remains the most frequent cause of CS.**

- Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to **acute MI,** and less frequently by;
  - cardiomyopathy or myocarditis
  - cardiac tamponade
  - arrhythmias or
  - critical valvular heart disease

- **Clinical features**
  - Most patients initially are;
    - **Dyspneic**
    - **appear pale**
    - **cold extremity**
    - **poor capillary refill**
    - **apprehensive and diaphoretic**
    - **mental status may be altered.**
  - **The pulse is typically weak and rapid** or occasionally severe bradycardia due to high-grade heart block may be present.
  - **BP** is typically reduced **(<90 mmHg**; or catecholamines required to maintain blood pressure >90 mmHg), but occasionally BP may be maintained by very high systemic vascular resistance.
  - **Tachypnea and jugular venous distention** may be present.
  - **Typically, there is a weak apical pulse and soft S1,** and S3 gallop may be audible.
  - **Acute, severe MR** and VSR usually are associated with characteristic systolic murmurs.
  - **Crackles** are audible in most patients with LV failure.
  - **Oliguria/anuria is common.**

- **Diagnosis**
- For these unstable patients, **supportive therapy must be initiated simultaneously with diagnostic evaluation.**
- **A focused history and physical examination** should be performed along **with ECG, chest X-ray, and blood specimens** to the laboratory
- Initial **Echo** is an invaluable tool to elucidate the underlying cause of CS.

Management of cardiogenic shock

- In addition to the **usual treatment of acute MI**, initial therapy is **aimed at**;
  - maintaining adequate systemic and coronary perfusion by raising the blood pressure with vasopressors and adjusting volume status to a level that ensures optimum LV filling pressure
  - Generally adequate perfusion occurs with a mean arterial BP of 60 - 65 mmHg or a systolic BP ~90 mmHg.

- Administer O2 if $SaO_2<90\%$
    - Hypoxemia and acidosis need to be corrected; up to 90% of patients require ventilatory support, decreasing the stress from increased work of breathing
    - Often CS patients require early mechanical ventilation (~80%) for management of acute hypoxemia, increased work of breathing, and hemodynamic instability;
- Administer NS **250ml over 30 min** and see the change in BP, UOP and worsening of HF.
    - ✓ If BP improves then consider hypovolemic shock and continue slowly replacing the fluid with NS.
    - ✓ If there is no response to fluid or worsening heart failure, use either of the following vasopressor therapies:

First line

- **Norepinephrine (noradrenaline)**
    - 0.2 µg/kg/min escalated to 1µg/kg/min by doubling the dose q20 min until BP> 90/60 mmHg (or 2 to 4 µg/min and titrated upward based on blood pressure).
    - **Maintain the dose that maintained the BP> 90/60 mmHg for 6hrs**, then you will deescalate as the same as the escalation *(look at adrenaline drip preparation below).*
    - *We recommend to use the above dose; in another reference you may see the dose as: 0.5 - 1 mcg/minute and titrate to desired response; 8-30 mcg/minute is usual range*

Alternative

- **Dopamine**
    - **5 - 20 µg/kg/min IV diluted with dextrose 5% in Water (D5W), or in sodium chloride solution 0.9%(NS)**
    - **infusion at 5µg/kg/min and escalate up to 40ug/kg/min by doubling the dose q20 min until BP> 90/60 mmHg.**
    - Maintain the dose that maintained the BP> 90/60 mmHg for 6hrs, then you will deescalate as the same as the escalation *(look at dopamine drip preparation below)*.
- **Dobutamine**
    - Start with 2.5 µg/kg per min to be titrated up to 40**µg**/kg/min IV diluted in dextrose 5%.
    - **Never initiate Dobutamine alone in a patient with cardiogenic shock and Systolic BP< 70**
- **Adrenaline** infusion:
    - 0.01-0.5 µg/kg/minute (7-35 µg/minute in a 70 kg patient); titrate to desired response

✓ **Maintain the dose of vasopressor that maintained the BP> 90/60 mmHg**

for 6hrs *(what is the reason behind maintaining for 6hr's?),* then you will taper the dose of vasopressor in the same way as it was escalated if BP is maintained. *(look at dopamine and adrenaline drip preparation below).*
  - ✓ If myocardial infarction suspected aspirin should be loaded and immediate reperfusion.
  - ✓ If patient has concomitant pulmonary edema resulting in hypoxia
    - Continuous infusion of Lasix (frusemide) started at 5-10 mg/hr should be started through another IV line (escalate dose based on Blood Pressure).
- ✓ More frequent follow up of V/S, SO2 and UOP q 20-30min until patient stabilize
- ✓ Further follow up and management is similar to other heart failure syndromes.
- ✓ Moderate glucose control (≤180 mg/dL) should be a goal and hypoglycemia must be avoided.
- ✓ Negative ionotropic agents should be discontinued.
- ✓ Recurrent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment
- ✓ Bradyarrhythmia's may require transvenous pacing.

5 x 5 ml Ampoules
Dopamine Hydrochloride
Injection USP 40 mg
FLASTROPIN
IV Infusion only
5 ml

Dopamine drip preparation

- 1 ampoule of dopamine = 5ml/each ml contains 40mg/ = 200mg = 200,000 μg
- Dose to be administered = 5 μg/kg/min up to 40 μg/kg/min

(N.B. *dose range may differ from reference to reference)*

Since weight measurement in shock pt is difficult, you may take approximated weight (let's say 50kg weight for this calculation, this will make 5 μg/kg/min =250 μg)

- ✓ Let's say we add 4 ampoules (800,000 μg) of dopamine in 1000ml of NS or D5W. the question will be in how many ml of NS and at what rate (drop) we get 250 μg
- ✓ 1000ml = 800,000 μg

?? = 250 μg

This will give us 0.3125 ml

1ml = 20 drops

0.3125ml = ???

This will give us 6 drops (i.e. 6 drops will contain 5 μg/kg/min of dopamine for this particular patient)

How shall we proceed?

- ✓ We will measure BP every 20 minutes
- ✓ If BP <90/60(not responding) double the dose like below
  - ☛ 6dpm (5 μg/kg/min)
  - ☛ 12dpm (10 μg/kg/min)
  - ☛ 24dpm (20 μg/kg/min)
  - ☛ 48dpm (40 μg/kg/min)

better to put the dose in μg/kg/min than dpm in follow up

📖 Maximum dose; some experts say you can go up to 50 μg/kg/min

For how long shall we maintain or when to deescalate?

- ✓ From my practical experience, If BP ≥ 90/60, we maintain the drop for 6 hr's before starting de-escalation (what is the reason behind?)
- ✓ How to deescalate? → de-escalate as it was escalated
  - ☛ 48dpm (40 μg/kg/min)
  - ☛ 24dpm (20 μg/kg/min)
  - ☛ 12dpm (10 μg/kg/min)
  - ☛ 6dpm (5 μg/kg/min)
  - ☛ stop

Source → https://t.me/Debolteam

Table*; Calculated dose and drop per minute of dopamine based on the above calculation

Weight in Kg	Dopamine dose (µg/min)						
	3	5	10	15	20	30	40
	Drop/minute of dopamine						
50	3 drops	5 drops	10 drops	15 drops	20 drops	30 drops	40 drops
60	3.5 drops	6 drops	12 drops	18 drops	24 drops	36 drops	48 drops
70	4.2 drops	7 drops	14 drops	21 drops	28 drops	42 drops	56 drops
80	4.8 drops	8 drops	16 drops	24 drops	32 drops	48 drops	64 drops
90	5.4 drops	9 drops	18 drops	27 drops	36 drops	54 drops	72 drops
100	6 drops	10 drops	20 drops	30 drops	40 drops	60 drops	80 drops

*Prepared by; Dr. Genet Kifle (MD, Emergency and critical care consultant)

Adrenaline drip preparation

10 x 1 ml Ampoules
Adrenaline Injection BP 1mg
For SC / IM / IV Use after dilution
1 ml
OMT

- 1 ampoule of adrenaline = 1ml = 1mg (1:1,000); there is also 0.1mg/1ml (1:10,000) preparation
- Dose to be administered = 0.01 µg/kg/min up to 0.5 µg/kg/min for cardiogenic shock (we are using 0.2 µg/kg/min as routine in our setup)

  (N.B. *dose range may differ from reference to reference)*

Let's take 50kg weight for this calculation, this will make 0.2 µg/kg/min =10 µg

- ✓ Let's say we add 4 ampoules (4mg = 4,000 µg) of adrenaline in 250ml of NS or D5W. the question will be in how many ml of NS and at what rate (drop) we get 10 µg
- ✓ 250ml = 4,000 µg
  ?? = 10 µg

This will give us 0.625 ml

1ml = 20 drops
0.625ml = ???

This will give us ≅12 drops (i.e. 12 drops will contain 0.2 µg/kg/min of adrenaline for this particular patient)

How shall we proceed?

- ✓ We will measure BP every 20 minutes
- ✓ If BP <90/60 double the dose like below
  - ☛ 12dpm (0.2 µg/kg/min)
  - ☛ 24dpm (0.4 µg/kg/min)
  - ☛ 48dpm (0.8 µg/kg/min)

  } better to put the dose in µg/kg/min than dpm in follow up
- ✓ If BP ≥ 90/60, maintain the drop for 6 hr's before starting de-escalation
- ✓ de-escalate as it was escalated
  - ☛ 48dpm (0.8 µg/kg/min)
  - ☛ 24dpm (0.4 µg/kg/min)
  - ☛ 12dpm (0.2 µg/kg/min)
  - ☛ stop

1 ampoule of Noradrenaline(2mg/ml) = 4mg = 2ml = 4,000 µg (you can prepare the drip based on the above methods). Initial dose; 0.2 µg/kg/min

Normit
℞
4 mg/2ml
Sterile Noradrenaline Concentrate IP
Normit
mits
Normit

Septic shock

- In **distributive shock**, there is relative intravascular volume depletion due to marked systemic vasodilatation. This is most commonly seen in septic shock.
- Anaphylaxis, neurogenic shock and adrenal insufficiency are additional causes of distributive shock.
- What is sepsis? (refer under miscellaneous Section of Nitsibin; click here → Sepsis)

Management of septic shock

- Principles of management
    - **IV Fluids**
    - **broad spectrum antibiotics**
    - **vasopressor therapy.**
    - **Steroids**
- Adequate organ system perfusion with IV fluids (large volume of IV fluids are required in septic shock patients).
    - ✓ Initial fluid bolus of 20 mL/kg of RL or NS.
    - ✓ Repeat 2 boluses of 20ml/kg with target of SBP >90mmhg, and MAP>60mmhg.
    - ✓ If goal not achieved, start vasopressors.
    - ✓ In general, most patients with septic shock are expected to take around 5-6 liter of IV fluids within 24 hours.
- Start Empiric therapy with broad spectrum antibiotics in septic shock patients as soon as possible at least within 01 hour of the clinical suspicion of septic

shock and draw blood for culture.

- If non responsive to fluid resuscitation administer vasopressor therapy.

  First line

  - ✓ **Norepinephrine (noradrenaline),** Initial: 0.5-1mcg/minute and titrate to desired response; 8-30 mcg/minute is usual range

  Alternatives

  - ✓ **Dopamine**, 5-50 mcg/kg/min IV diluted with dextrose 5% in Water, or in sodium chloride solution 0.9%;
  - ✓ **Adrenaline, I.V. infusion:** Initial: 0.1-0.5 mcg/kg/minute (7-35 mcg/minute in a70 kg patient); titrate to desired response
- If the Blood pressure doesn't respond for the initial management with vasopressors and fluids
  - ✓ Hydrocortisone, 50 mg IV QID (when vasopressor dependent or)

Adrenal crisis

- ✓ **NS Large volumes (1 to 3 liters)** or 5 % dextrose in 0.9% percent saline should be infused intravenously /**infusion like hypovolemic shock.**
- ✓ **Hydrocortisone**, 200mg, IV, stat then 100mg, IV, QID
- ✓ **start the vasopressor management as a septic shock protocol if the BP doesn't respond to IV fluids and steroid therapy.**

Refer sepsis under short case of nitsibin for more (click here → Sepsis*)*

3.2 Hypoglycaemia

→ Refer under long case of DM (click here → Hypoglycaemia)

3.3 DKA

→ Refer under long case of DM (click here → DKA and HHS)

3.4 Thyroid storm

→ Refer under miscellaneous section, from short case of Nitsibin (click here → *Thyroid storm / thyrotoxic crisis*)

3.5 CVA (stroke)

→ Refer under long case of Stroke (click here → Chapter 6; Stroke)

3.6 Seizure and epilepsy (የሚጥል በሽታ)

Dr. Asmare. W, Dr. Mulualem. G

- **A seizure** (from the Latin sacire, “to take possession of”) **is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain.**
- Depending on the distribution of discharges, this abnormal brain activity can have various manifestations, ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer.
- The meaning of the term seizure needs to be carefully distinguished from that of epilepsy.
- **Epilepsy** describes a condition in which a person has **recurrent seizures (two or more unprovoked seizures) due to a chronic, underlying process**.
- This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy.
- **Epilepsy refers to a clinical phenomenon rather than a single disease entity**, because there are many forms and causes of epilepsy. However, among the many causes of epilepsy there are various epilepsy syndromes in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology.
- **Epilepsy refers to a syndrome of recurrent, idiopathic seizures**.
- **Pseudo seizures** are not true seizures but are psychiatric in origin; are often difficult to distinguish from true seizures without an EEG.
- **So, Epilepsy considered in one of the following conditions**
    - At least **two unprovoked** (or reflex) seizures occurring > 24 hours apart.
    - One unprovoked (or reflex) seizure and **a probability of further seizures** similar to the general recurrence risk after two unprovoked seizures **(at least 60%),** occurring over the next 10 years.
    - **A known epilepsy syndrome.**

Definitions of Terminologies in seizure and epilepsy

- **Pre- Ictal**
    - Events that occur Immediately before the seizure, and include Aura and Prodromal symptoms/signs
- **Aura**
    - Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, or illusions that objects are growing smaller (micropsia) or larger (macropsia).
        - These **subjective, “internal” events that are not directly observable by someone else are referred to as auras**
- **Seizure (Ictal) semiology**

  - It is the sign and symptoms observed just before, during and immediately after the seizure occurrence.
  - Ictal Semiology means features occurring during the attack
    - Simple: Motor; Sensory; Autonomic; Psychic….
    - Complex: Motor; Sensory; Autonomic; Psychic….
  - Motor semiology: Motor manifestations refer to involvement of the musculature, which can be positive (increased muscle activity) or negative (decreased muscle activity)
    - simple motor refers to the contraction of a muscle or group of muscles that is usually stereotyped and does not include multiple phases.
    - Complex motor activity: Automatism
  - Motor semiologies can be tonic, myoclonic or clonic
    - **Tonic activity** which means a sustained increase in muscle contraction lasting up to minutes.
    - **A myoclonic jerk** refers to a very brief involuntary contraction usually lasting less than 100 micro sec.
    - **Clonic activity** refers to a regularly repetitive jerking that is prolonged
- **Post-Ictal features:**
  - Features occur after the seizure stops

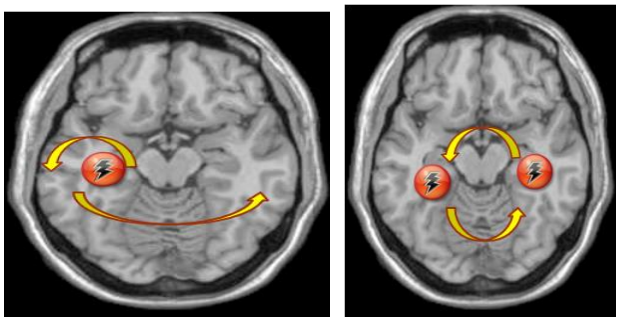
Epidemiology

- The incidence and prevalence of epilepsy **increase with age in adulthood and are highest in patients over 65 years.**
- The prevalence of epilepsy in older adults is approximately 2 - 5%
- The annual incidence of epilepsy rises with each decade over 60 years.
- Seizures in older patients are frequently underdiagnosed; hence, the incidence of epilepsy in older patients may be two to three times higher, with an incidence six to seven times greater than younger individuals.

Classification of seizures

- Determining the type of seizure that has occurred is essential for focusing the diagnostic approach on particular etiologies, selecting the appropriate therapy, and providing potentially vital information regarding prognosis.
- The International League against Epilepsy (ILAE) Commission on Classification and Terminology (2005 - 2009) has provided an updated approach to classification of seizures.
  - This system is based on the clinical features of seizures and associated electroencephalographic findings.

- **Focal seizures** originate within networks **limited to one cerebral hemisphere** (note that the term partial seizures is no longer used).
- **Generalized seizures** arise within and rapidly engage networks distributed **across both cerebral hemispheres**.
- Focal seizures are usually associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.



Picture; left) **Focal seizure,** right) **Generalized seizure**

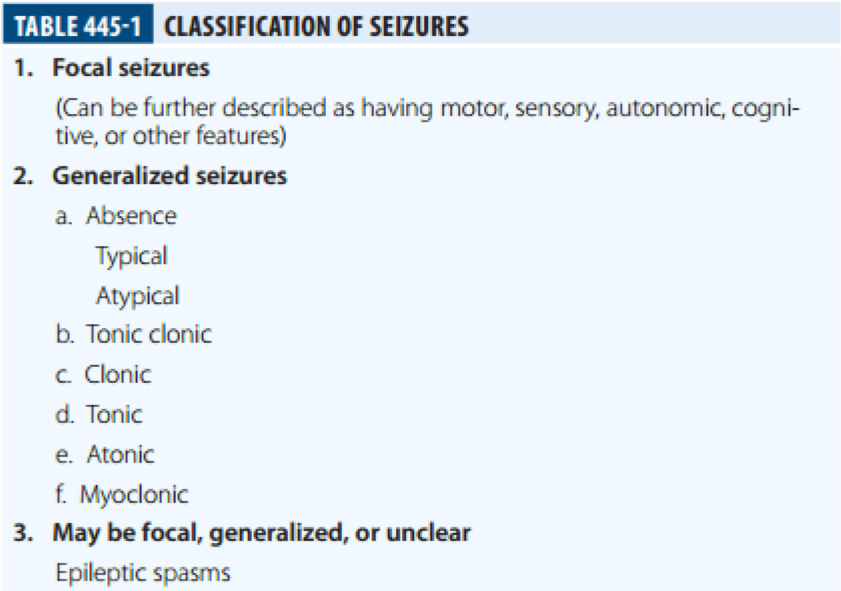


TABLE 445-1 CLASSIFICATION OF SEIZURES

1. **Focal seizures**
   (Can be further described as having motor, sensory, autonomic, cognitive, or other features)
2. **Generalized seizures**
   a. Absence
      Typical
      Atypical
   b. Tonic clonic
   c. Clonic
   d. Tonic
   e. Atonic
   f. Myoclonic
3. **May be focal, generalized, or unclear**
   Epileptic spasms

Focal seizures

- Focal seizures arise from a neuronal network either discretely localized within one cerebral hemisphere or more broadly distributed but still within the hemisphere.
- With the new classification system, the subcategories of “simple focal seizures” and “complex focal seizures” have been eliminated. Instead, depending on the

presence of cognitive impairment, they can be described as **focal seizures with or without dyscognitive features.**

- Focal seizures can also evolve into generalized seizures. In the past this was referred to as focal seizures with secondary generalization, but the new system relies on specific descriptions of the type of **generalized seizures that evolve from the focal seizure.**
- The routine interictal (i.e., between seizures) electroencephalogram (EEG) in patients with focal seizures is often normal or may show brief discharges termed epileptiform spikes, or sharp waves.
- Because focal seizures can arise from the medial temporal lobe or inferior frontal lobe (i.e., regions distant from the scalp), the EEG recorded during the seizure may be non-localizing. However, the seizure focus is often detected using sphenoidal or surgically placed intracranial electrodes.

Focal Seizures Without Dyscognitive Features

- Focal seizures can cause motor, sensory, autonomic, or psychic symptoms without impairment of cognition.
- For example, a patient having a focal motor seizure arising from the right primary motor cortex near the area controlling hand movement will note the onset of involuntary movements of the contralateral, left hand. These movements are typically clonic (i.e., repetitive, flexion/extension movements); pure tonic posturing may be seen as well.
- Since the cortical region controlling hand movement is immediately adjacent to the region for facial expression, the seizure may also cause abnormal movements of the face synchronous with the movements of the hand.
- Three additional features of focal motor seizures are worth noting.
  - 1st, in some patients, the abnormal motor movements may begin in a very restricted region such as the fingers and gradually progress (over seconds to minutes) to include a larger portion of the extremity. This phenomenon, known as a “Jacksonian march,” represents the spread of seizure activity over a progressively larger region of motor cortex.
  - 2nd, patients may experience a localized paresis **(Todd’s paralysis)** for minutes to many hours in the involved region following the seizure.
  - 3rd, in rare instances, the seizure may continue for hours or days. This condition, termed *epilepsia partialis continua*, is often refractory to medical therapy.
- Focal seizures may also manifest as;
  - changes in somatic sensation (e.g., paresthesias)
  - vision (flashing lights or formed hallucinations)
  - equilibrium (sensation of falling or vertigo), or
  - autonomic function (flushing, sweating, piloerection).

- Focal seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or higher cortical function (psychic symptoms). This includes;
  - the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds)
  - an epigastric sensation that rises from the stomach or chest to the head.
- *Auras*.

Focal Seizures with Dyscognitive Features

- Focal seizures may also be accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment.
- The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase.
- The seizures frequently begin with an aura (i.e., a focal seizure without cognitive disturbance) that is stereotypic for the patient.
- The start of the **ictal phase** is often **a sudden behavioral arrest or motionless stare,** which marks the onset of the period of impaired awareness.
- The behavioral arrest is usually accompanied by *automatisms*, which are involuntary, automatic behaviors that have a wide range of manifestations.
  - Automatisms may consist of very basic behaviors such as chewing, lip smacking, swallowing, or "picking" movements of the hands,
    or more elaborate behaviors such as a display of emotion or running.
- **The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour**.
- Examination immediately following the seizure may show an **anterograde amnesia** or, in cases involving the dominant hemisphere, **a postictal aphasia**.

Evolution of Focal seizures to generalized seizures

- Focal seizures can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety.
- This evolution is observed frequently following focal seizures arising from a focus in the frontal lobe, but may also be associated with focal seizures occurring elsewhere in the brain.
- Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis.
- Nonetheless, **distinguishing between these two entities is extremely important**, because there may be substantial differences in the evaluation and treatment of epilepsies associated with focal versus generalized seizures.

Generalized seizures

- Generalized seizures are thought to arise at some point in the brain but immediately and rapidly engage neuronal networks in both cerebral hemispheres.
- Several types of generalized seizures have features that place them in distinctive categories and facilitate clinical diagnosis.

Typical Absence Seizures

- Typical absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control.
- The seizure **typically lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion**.
- Although the brief loss of consciousness may be clinically in apparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as **rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands.**
- Typical absence seizures are associated with a group of genetically determined epilepsies with **onset usually in childhood (ages 4 - 8 years**) or early adolescence and are the main seizure type in 15- 20% of children with epilepsy.
- The **seizures can occur hundreds of times per day**, but the child may be unaware of or unable to convey their existence.
- Because the clinical signs of the seizures are subtle, especially to parents who may not have had previous experience with seizures, it is not surprising that the first clue to absence epilepsy is often unexplained "**daydreaming**" and a **decline in school performance** recognized by a teacher.
- The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background.

Atypical Absence Seizures

- Atypical absence seizures have features that deviate both clinically and electro physiologically from typical absence seizures.
- For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is accompanied by more obvious motor signs that may include focal or lateralizing features.
- The EEG shows a generalized, slow spike-andwave pattern with a frequency of $\leq$2.5 per second, as well as other abnormal activity.

Generalized, Tonic-Clonic Seizures

- Generalized-onset tonic-clonic seizures are the main seizure type in ~10% of all persons with epilepsy.
- They are also the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings.
- The initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event.
- Tonic contraction of the muscles of expiration and the larynx at the onset will produce **a loud moan or "ictal cry."**
- **Respirations are impaired, secretions pool in the oropharynx, and cyanosis** develops.
- Contraction of the jaw muscles may cause **biting of the tongue**.
- A marked enhancement of sympathetic tone leads to **increases in heart rate, blood pressure, and pupillary size.**
- After 10 - 20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by the superimposition of periods of muscle relaxation on the tonic muscle contraction.
- The periods of relaxation progressively increase until the end of the ictal phase, which usually lasts **no more than 1 min.**
- The postictal phase is characterized by **unresponsiveness, muscular flaccidity, and excessive salivation** that can cause stridorous breathing and partial airway obstruction.
- **Bladder or bowel incontinence** may occur at this point.
- Patients gradually **regain consciousness over minutes to hours,** and during this transition, there is typically a period of **postictal confusion**.
- Patients subsequently complain of **headache, fatigue, and muscle ache** that can last for many hours.
- The duration of impaired consciousness in the postictal phase can be extremely long (i.e., many hours) in patients with prolonged seizures or underlying CNS diseases such as **alcoholic cerebral atrophy**.
- There are a number of **variants of the generalized tonic-clonic seizure**, including
  - pure tonic and
  - pure clonic seizures.
- **Brief tonic seizures** lasting only a few seconds are especially noteworthy since they are usually associated with specific epileptic syndromes having mixed seizure phenotypes, such as the Lennox-Gastaut syndrome.

Atonic Seizures

- Atonic seizures are characterized by **sudden loss of postural muscle tone lasting 1- 2 s.**

- **Consciousness is briefly impaired**, but there is usually **no postictal confusion.**
- A very brief seizure may cause only **a quick head drop or nodding movement**, whereas **a longer seizure will cause the patient to collapse**.
  This can be extremely dangerous, because there is a substantial risk of direct **head injury with the fall.**
- The EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone.
- Similar to pure tonic seizures, atonic seizures are usually seen in association with known epilepsy syndromes.

Myoclonic Seizures

- Myoclonus is a sudden and **brief muscle contraction** that may involve one part of the body or the entire body.
- A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep.
- Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury.
- Myoclonic seizures usually coexist with other forms of generalized seizures but are the predominant feature of juvenile myoclonic epilepsy.

Currently Unclassified seizures

- Not all seizure types can be designated as focal or generalized, and they should therefore be labeled as “unclassifiable” until additional evidence allows a valid classification.
- **Epileptic spasms** are such an example.
  These are characterized by a briefly sustained flexion or extension of predominantly proximal muscles, including truncal muscles.
  Epileptic spasms occur predominantly **in infants** and likely result from differences in neuronal function and connectivity in the immature versus mature CNS.

Epilepsy syndromes

- Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence (e.g., through clinical, EEG, radiologic, or genetic observations) to suggest a common underlying mechanism
- Examples include[17]
  - **Juvenile myoclonic epilepsy**
  - **Lennox-Gastaut syndrome**
  - **Mesial temporal lobe epilepsy syndrome**

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[17] Reading assignment from Harrison 20th edition, part 13, section 2, Chapter 418

Causes of seizures and epilepsy

- Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS.
- Given the numerous properties that control neuronal excitability, it is not surprising that there are many different ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy.
- Causes of seizures can be remembered by the four M's and the four I's
- The four M's
    - **Metabolic and electrolyte disturbances**:
        - Hyponatremia
        - Hypoglycemia or hyperglycemia
        - Hypocalcemia
        - Uremia
        - Thyroid storm
        - Hyperthermia (Febrile seizure is common in children)
    - **Mass lesions**:
        - Brain mass (primary or secondary brain tumors)
        - Hemorrhages (ICH, SDH, EDH).
    - **Missing drugs (Noncompliance) with anticonvulsants** in patients with epilepsy. This is the most common reason for poor seizure control in epileptics.
    - **Miscellaneous**
        - Eclampsia
        - Hypertensive encephalopathy; severe hypertension can cause cerebral edema
        - Acute withdrawal from alcohol
        - Drugs (e.g. Benzodiazepines, Barbiturates).
        - Vascular malformation
- The four I's
    - **Intoxications**
        - Cocaine
        - Lithium
        - Theophylline
        - Carbon monoxide poisoning.
    - **Infections**
        - Malaria
        - Meningitis (bacterial or viral)
        - Brain abscess
        - Sepsis.
    - **Ischemia;** common cause of seizure in elderly patients.

        - Stroke
        - TIA
    - Increased ICP:
        - Trauma (SDH, EDH)
        - Cerebral edema of different causes

Another Mnemonics for etiology of seizure → Vitamins$_2$

- Vascular: stroke, hemorrhage, hypertension, AVM (Arteriovenous malformation) in children
- Infections: meningitis, encephalitis
- Trauma
- Autoimmune: SLE, vasculitis, ADEM (Acute disseminated encephalomyelitis)
- Metabolic/toxic
- Idieopathic
- Neoplastic
- Structural: prior stroke, cortical malformation in pediatrics age
- Syndrome: Epilepsy syndromes, genetic disorder

Causes of seizure according to Age

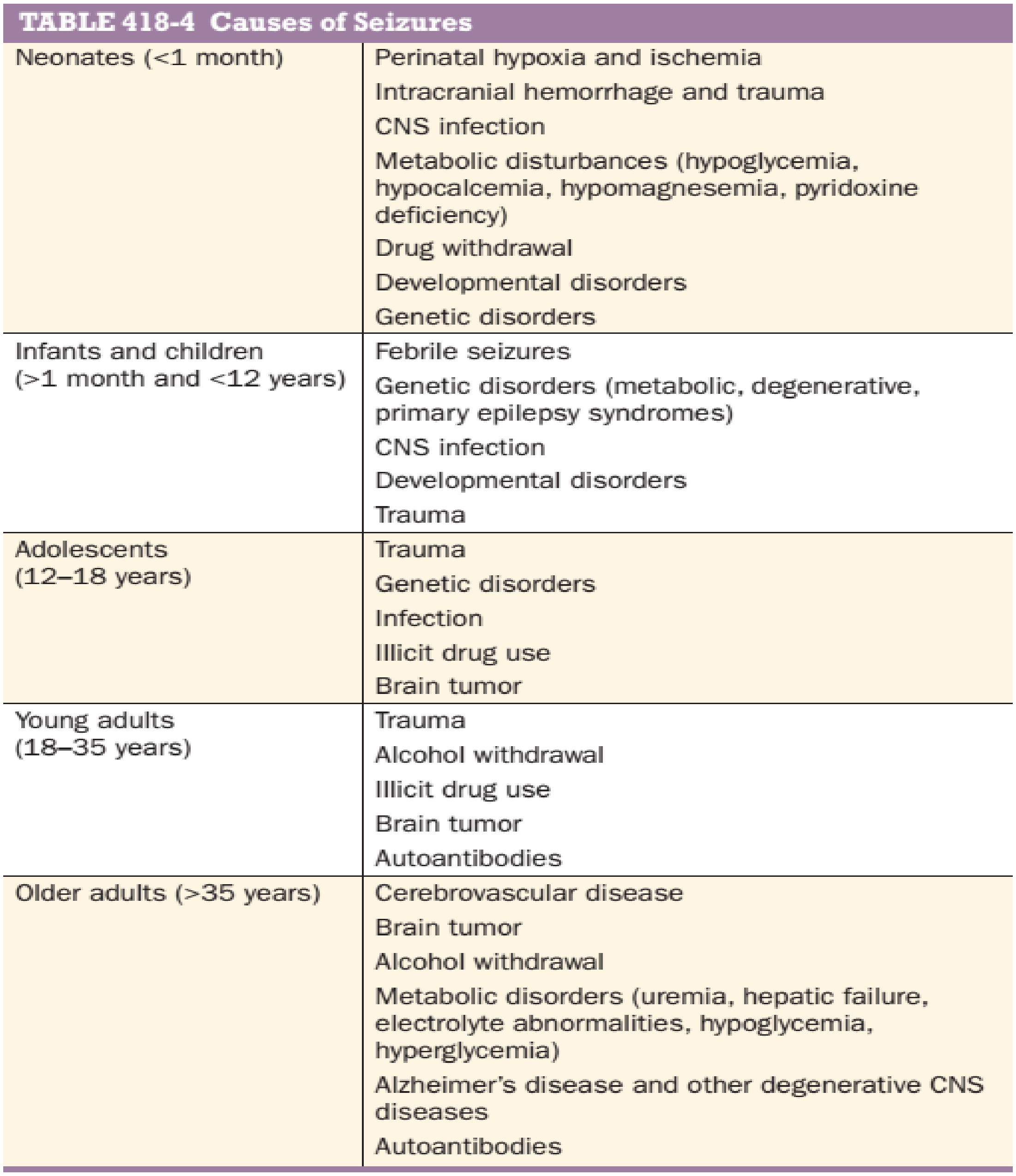


TABLE 418-4 Causes of Seizures

Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer's disease and other degenerative CNS diseases Autoantibodies

- **Head trauma** is a common cause of epilepsy in adolescents and adults.
- The head injury can be caused by a variety of mechanisms, and the likelihood of developing epilepsy is strongly correlated with the severity of the injury.
- A patient with a ***penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia*** has a **30 - 50%** risk of developing epilepsy
- A patient with a ***closed head injury and cerebral contusion has*** a **5-25%** risk.
- Recurrent seizures usually develop **within 1 year** after head trauma, although intervals of >10 years are well known.

Diagnosis and Investigations

- Seizure and epilepsy are a Clinical diagnosis (see approach to the patient with active **seizure below)**
- If the patient has a known seizure disorder (epileptic), check adherence.
- If the patient history is unclear or if this is the patient's first seizure, do the following Investigations;
  - RBS
  - CBC
  - Electrolytes
  - LFT
  - RFT (BUN and creatinine)
  - Urinalysis
  - EEG
    - Although the EEG is the most helpful diagnostic test in the diagnosis of a seizure disorder an abnormal EEG pattern alone is not adequate for the diagnosis of seizures.
    - A normal EEG in a patient with a first seizure is associated with a lower risk of recurrence.
  - LP and blood cultures → if patient is febrile
  - Brain imaging
    - Almost all patients with new-onset seizures should have a brain imaging study to determine whether there is an underlying structural abnormality that is responsible.
    - The only potential exception to this rule is children who have an unambiguous history and examination suggestive of a benign, generalized seizure disorder such as absence epilepsy.
    - MRI has been shown to be superior to CT for the detection of cerebral lesions associated with epilepsy.

Differential Diagnosis of seizures

- **Syncope**
  - The diagnostic dilemma encountered most frequently is the distinction between a generalized seizure and syncope.
  - Characteristics of a seizure include the presence of an ***aura, cyanosis, unconsciousness, motor manifestations lasting >15 s, postictal disorientation, muscle soreness, and sleepiness***. In contrast, a syncopal episode is more likely if the event was ***provoked by acute pain or anxiety or occurred immediately after arising from the lying or sitting position***.
  - Patients with syncope often describe a stereotyped transition from consciousness to unconsciousness that includes tiredness, sweating, nausea, and tunneling of vision, and they experience a relatively brief loss of consciousness.
- **Psychogenic seizures**
  - Psychogenic seizures are nonepileptic behaviors that resemble seizures.

  - They are often part of a conversion reaction precipitated by underlying psychological distress.
  - Certain behaviors such as side to-side turning of the head, asymmetric and large-amplitude shaking movements of the limbs, twitching of all four extremities without loss of consciousness, and pelvic thrusting are more commonly associated with psychogenic rather than epileptic seizures.
- **TIA (Transient ischemic attack)**
- **Migraine**
- **Acute psychosis**

3.6.1 Status epilepticus and management of Active seizure in emergency setup

- Status epilepticus refers to **continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period.**
- Status epilepticus has numerous **subtypes**, including
  - **Generalized convulsive status epilepticus (GCSE)** (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements)
  - **Nonconvulsive status epilepticus** (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities).
- The **duration** of seizure activity sufficient to meet the definition of status epilepticus **has traditionally been specified as 15 - 30 min**. However, a more **practical definition is** to consider status epilepticus as a situation in which **the duration of seizures prompts the acute use of anticonvulsant therapy**.
- For **GCSE**, duration is typically when seizures last **beyond 5 min.**
- GCSE is an emergency and must be treated immediately, because cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury.
- The treatment of nonconvulsive status epilepticus is thought to be less urgent than GCSE, because the ongoing seizures are not accompanied by the severe metabolic disturbances seen with GCSE.

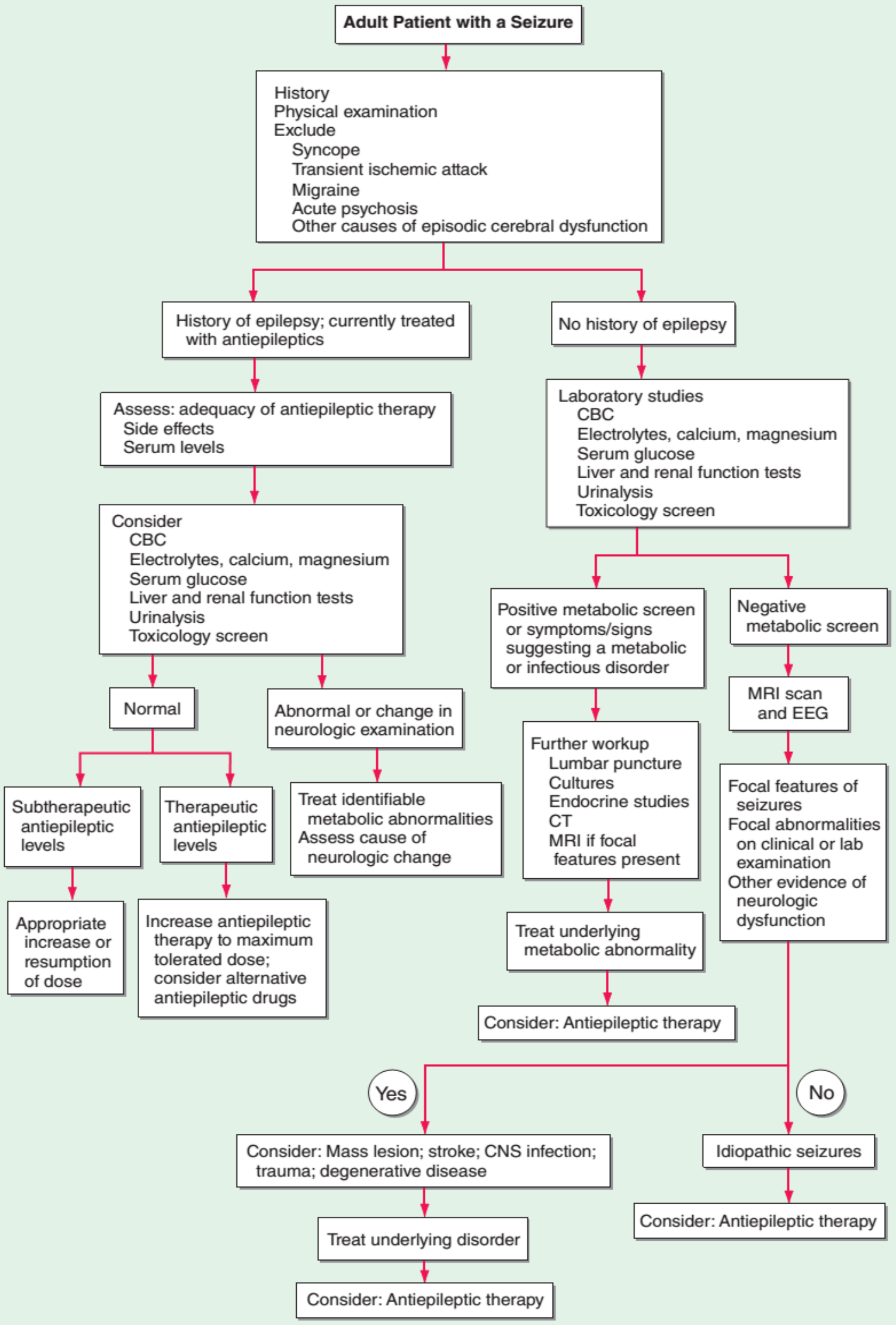
Approach to the patient with active **seizure**

(See the algorism's below)

- When a patient presents shortly after a seizure, the first priorities are attention to **ABC of Life** including;
  Vital signs
  Respiratory and cardiovascular support, and
  Treatment of seizures if they resume
- Life-threatening conditions such as CNS infection, metabolic derangement, or drug toxicity must be recognized and managed appropriately.

- When the patient is not acutely ill, the evaluation will initially focus on whether there is a history of earlier seizures
- If this is the first seizure, then the emphasis will be to:
  - Establish whether the reported episode was a seizure rather than another paroxysmal event
    - Seizures frequently occur out-of-hospital, and the patient may be unaware of the ictal and immediate postictal phases; thus, witnesses to the event should be interviewed carefully.
  - Determine the cause of the seizure by identifying risk factors and precipitating events
    - Clues for a predisposition to seizures include a history of febrile seizures, earlier auras or brief seizures not recognized as such, and a family history of seizures.
    - Epileptogenic factors such as prior head trauma, stroke, tumor, or CNS infection should be identified.
    - Precipitating factors such as sleep deprivation, systemic diseases, electrolyte or metabolic derangements, acute infection, drugs that lower the seizure threshold, or alcohol or illicit drug use should also be identified.
  - Decide whether anticonvulsant therapy is required in addition to treatment for any underlying illness.
- In the patient with prior seizures or a known history of epilepsy, the evaluation is directed toward:
  - Identification of the underlying cause and precipitating factors, and
  - Determination of the adequacy of the patient's current therapy.
- While managing active seizure and life-threatening conditions, pertinent and targeted physical examination should be done including a search for underlying cause and precipitants
- All patients require a complete neurologic examination, with particular emphasis on eliciting signs of cerebral hemispheric disease

ALGORITHM FOR THE ADULT PATIENT WITH A SEIZURE


Adult Patient with a Seizure
History
Physical examination
Exclude
Syncope
Transient ischemic attack
Migraine
Acute psychosis
Other causes of episodic cerebral dysfunction
History of epilepsy; currently treated with antiepileptics
No history of epilepsy
Assess: adequacy of antiepileptic therapy
Side effects
Serum levels
Laboratory studies
CBC
Electrolytes, calcium, magnesium
Serum glucose
Liver and renal function tests
Urinalysis
Toxicology screen
Consider
CBC
Electrolytes, calcium, magnesium
Serum glucose
Liver and renal function tests
Urinalysis
Toxicology screen
Positive metabolic screen or symptoms/signs suggesting a metabolic or infectious disorder
Negative metabolic screen
Normal
Abnormal or change in neurologic examination
MRI scan and EEG
Further workup
Lumbar puncture
Cultures
Endocrine studies
CT
MRI if focal features present
Subtherapeutic antiepileptic levels
Therapeutic antiepileptic levels
Treat identifiable metabolic abnormalities
Assess cause of neurologic change
Focal features of seizures
Focal abnormalities on clinical or lab examination
Other evidence of neurologic dysfunction
Appropriate increase or resumption of dose
Increase antiepileptic therapy to maximum tolerated dose; consider alternative antiepileptic drugs
Treat underlying metabolic abnormality
Consider: Antiepileptic therapy
Yes
No
Consider: Mass lesion; stroke; CNS infection; trauma; degenerative disease
Idiopathic seizures
Treat underlying disorder
Consider: Antiepileptic therapy
Consider: Antiepileptic therapy

Indications for hospitalization

- Patient with first time seizure with
  - ✓ prolonged post ictal phase
  - ✓ incomplete recovery
  - ✓ serious seizure related injuries
- Status epilepticus

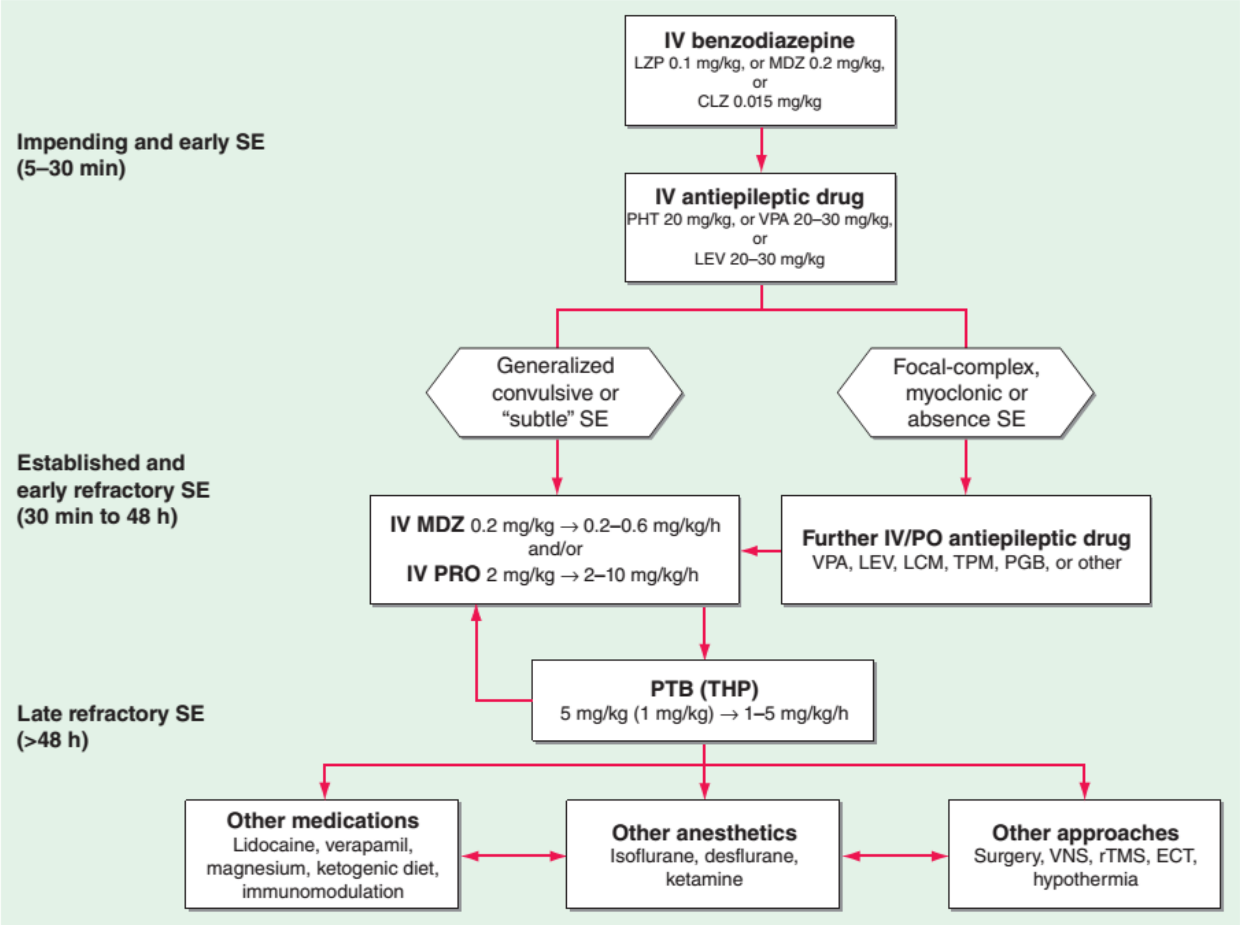
- Presence of neurologic or systemic disease which requires additional evaluation and treatment.

Treatment algorism of Active generalized tonic-clonic seizure and SE in our setup

Time	Medications	Other simultaneous medical managements
Impending and early SE **(within 5 - 30 min)**	✓ **Diazepam 0.15 to 0.2 mg/kg (max; 10mg), IV** (repeat once if no response after 5 minutes) • If no IV access, **Diazepam 0.2 to 0.5 mg/kg (max; 20mg), rectally** (The parenteral formulation of diazepam may be given rectally if rectal gel is not available) • Additional drug therapy may not be required if seizure stop or the etiology of SE is rapidly corrected If seizure continues ↓ ✓ Phenytoin, 20mg/kg, IV loading (at a maximum rate of 50mg/min) or the same dose of crushed tablets via NG tube (the usual loading dose is 1g, PO, stat) or ✓ valproic acid, 20-30mg/kg If seizure continues ↓ ✓ Phenytoin, 5 to 10 mg/kg, IV, 10 minutes after the loading dose (at a maximum rate of 50mg/min) or the same dose of crushed tablets via NG tube (the usual maintenance dose is 100 mg, PO, TID or QID) If seizure continues ↓ ✓ Phenobarbitone, 20mg/kg, IV (at a maximum rate of 60mg/min) or the same dose of crushed tablets via NG tube If seizure continues ↓	✓ ABC of life • Remove sharp and dangerous materials from the surrounding • Position the patient to lateral side to avoid aspiration • Put the patient in the recovery position if S/he loses consciousness • Start oxygen • Airway compromise is an indication for intubation • Secure IV line • Don't hold the patient to stop the seizure episode ✓ Do RBS • Give 50 ml of 50% dextrose IV bolus if low or Unknown • In our setup we use, 3 vial (60ml) of D40 since 50% dextrose is not available ✓ Continuous monitoring of Vital signs, O_2 and ECG (if indicated) ✓ Obtain laboratory tests ❖ CBC ❖ Electrolytes ❖ LFT ❖ RFT (BUN and creatinine)

Established and early refractory SE **(30 min to 48 h)**	✓ Phenobarbital, 15 to 20 mg/kg (infused at 50 to 100 mg/minute) or the same dose of crushed tablets via NG tube • If necessary, may repeat once after 10 minutes with an additional 5 to 10 mg/kg • Additional respiratory support may be required particularly when maximizing loading dose or if concurrent sedative therapy. • Repeat doses administered sooner than 10 to 15 minutes may lead to CNS depression. If seizure continues	✓ If still sizing after 30 minutes, perform EEG (If possible) when convulsive activity is controlled ✓ Begin continuous EEG if patient does not awaken rapidly or if continuous IV treatment is used (if available and performed with experienced neurologist)
Late refractory SE **(>48 h)**	✓ Midazolam, IV, loading dose: 0.2 mg/kg followed by a continuous infusion 0.2 - 0.6 mg/kg/h and/or ✓ Induce anesthesia with Propofol, IV loading dose 2 mg/kg, then Continuous infusion of 2 - 10 mg/kg/h or ✓ Phenobarbital (see the above description)	
General advice after stabilization healthy lifestyle with good sleep habits Avoid unsafe activities e.g. swimming alone, mountain climbing, driving car Take showers rather than baths. avoidance of excessive alcohol and caffeine. Consequences of poor drug compliance		

Pharmacologic treatment of generalized tonic-clonic status epilepticus (GTCSE) in western setups


IV benzodiazepine
LZP 0.1 mg/kg, or MDZ 0.2 mg/kg, or CLZ 0.015 mg/kg
Impending and early SE (5–30 min)
IV antiepileptic drug
PHT 20 mg/kg, or VPA 20–30 mg/kg, or LEV 20–30 mg/kg
Generalized convulsive or "subtle" SE
Focal-complex, myoclonic or absence SE
Established and early refractory SE (30 min to 48 h)
IV MDZ 0.2 mg/kg → 0.2–0.6 mg/kg/h and/or IV PRO 2 mg/kg → 2–10 mg/kg/h
Further IV/PO antiepileptic drug
VPA, LEV, LCM, TPM, PGB, or other
Late refractory SE (>48 h)
PTB (THP)
5 mg/kg (1 mg/kg) → 1–5 mg/kg/h
Other medications
Lidocaine, verapamil, magnesium, ketogenic diet, immunomodulation
Other anesthetics
Isoflurane, desflurane, ketamine
Other approaches
Surgery, VNS, rTMS, ECT, hypothermia

Figure; Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fos-phenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid.

3.6.2 Treatment of Seizures and epilepsy

- Therapy for a patient with a seizure disorder is almost always multimodal and includes
  - Treatment of underlying conditions that cause or contribute to the seizures
  - Avoidance of precipitating factors
  - Suppression of recurrent seizures by prophylactic therapy with antiepileptic medications (AED)
  - Surgery, and addressing a variety of psychological and social issues.

1. Treatment of underlying conditions

- If the sole cause of a seizure is a metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence.

- Therapy with antiepileptic drugs is usually unnecessary unless the metabolic disorder cannot be corrected promptly and the patient is at risk of having further seizures.

- If the apparent cause of a seizure was a medication (e.g., theophylline) or illicit drug use (e.g., cocaine), then appropriate therapy is avoidance of the drug;
  - there is usually no need for antiepileptic medications unless subsequent seizures occur in the absence of these precipitants.
- Seizures caused by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of the underlying lesion
- Most patients are therefore maintained on an antiepileptic medication for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure free.
- If seizures are refractory to medication, the patient may benefit from surgical removal of the epileptic brain region.

1. Avoidance of precipitating factors

- Unfortunately, little is known about the specific factors that determine precisely when a seizure will occur in a patient with epilepsy.
- Some patients can identify particular situations that appear to lower their seizure threshold; these situations should be avoided.
  - sleep deprivation should obviously be advised to maintain a normal sleep schedule.
  - Alcohol intake-modify their drinking habits accordingly.
  - Highly specific stimuli such as a video game monitor, music, or an individual's voice ("reflex epilepsy").
  - Stress → physical exercise, meditation and counseling

2. Antiepileptic drug (AED) therapy

- Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy.
- The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow.
- Seizure classification is an important element in designing the treatment plan, because some antiepileptic drugs have different activities against various seizure types.
- *Indication to start AED*

i. All non-symptomatic seizures two or more episodes
ii. **Indication to start AED after first unprovoked seizure**

- With Underlying lesions proven to be epileptogenic (i.e. Epileptiform abnormalities on interictal EEG)
- Remote cause: identified by history or neuroimaging (e.g. brain tumor, brain malformation, prior CNS infection)
- Abnormal neurologic examination
- A first seizure that occurs during sleep

iii. Other considerations for Indication of AED
  - Recurrent idiopathic seizure
  - Present with Status epileptics
  - Family history of epilepsy
  - Todd's paralysis
  - Potentially dangerous job workers (e.g. Machinery workers, Drivers, swimmers…) with idiopathic seizure

- *Patients with a history of seizures (epilepsy)*
  - **Start treatment with one AED**
  - If seizures persist, **increase the dosage of the first anticonvulsant** until signs of toxicity appear.
  - **Add a second drug if the seizures cannot be controlled with the drug of first choice.**
  - **If the patient remains seizure free, decrease the dose** of the medication(s) cautiously.
  - **Discontinuation** of AED can be considered if a patient has been completely **free of seizures for at least two year**; however, risk of recurrence of seizures should be discussed with the patient.
  - The **decision of discontinuation** should be individualized as the risk of recurrence is variable and it should be made **by a specialist (neurologist).**
- **Factors** to be taken into account in choosing drugs
  - Type of epilepsy
  - Age & sex
  - Other drugs, e.g. contraceptive pill
  - Other medical conditions, e.g. liver or renal dysfunction.
  - Race
  - Genotype of the epilepsy

AED choices

Table; Common AED choices for adults by seizure type in Ethiopia

Seizure type	First line options	Alternatives (second line)
Focal onset Seizure	Carbamazepine	Valproic acid
	Phenytoin	Phenobarbital
Generalized onset: Motor	Valproic acid	
	Phenobarbital	
	Carbamazepine	
	Phenytoin	
Absence	Valproic acid	phenobarbital, phenytoin

		Carbamazepine

AED choices for adults by seizure type in western setup[18]

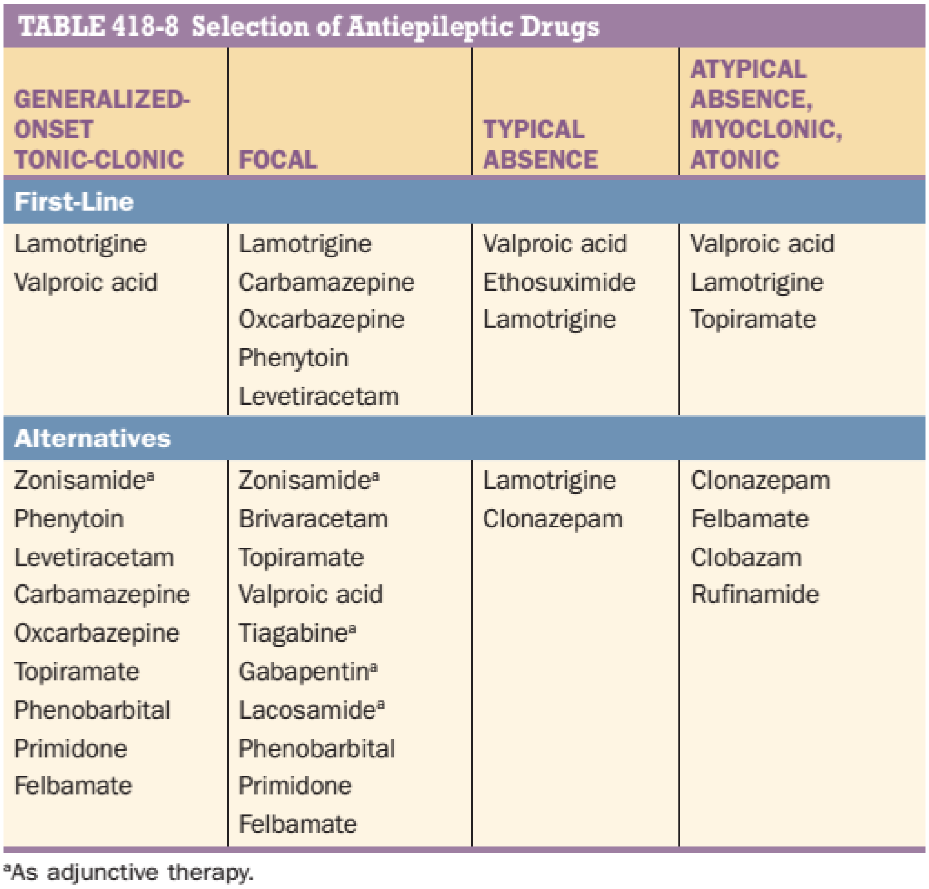


TABLE 418-8 Selection of Antiepileptic Drugs

GENERALIZED-ONSET TONIC-CLONIC	FOCAL	TYPICAL ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-Line			
Lamotrigine Valproic acid	Lamotrigine Carbamazepine Oxcarbazepine Phenytoin Levetiracetam	Valproic acid Ethosuximide Lamotrigine	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamide[a] Phenytoin Levetiracetam Carbamazepine Oxcarbazepine Topiramate Phenobarbital Primidone Felbamate	Zonisamide[a] Brivaracetam Topiramate Valproic acid Tiagabine[a] Gabapentin[a] Lacosamide[a] Phenobarbital Primidone Felbamate	Lamotrigine Clonazepam	Clonazepam Felbamate Clobazam Rufinamide

[a]As adjunctive therapy.

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[18] We mentioned these drugs for comparison with Ethiopia setup. Ethiopian standard consideration is based on availability of drugs. You can use those written in western setup if they are available.

Table. Common antiepileptic drug dosing

Drug	Initial dosage	Maximum dosage: not necessarily required	Titration and administration
Carbamazepine	100 - 200 mg, PO, BID	2,400 mg daily (usual effective dose 400 -1200mg/day)	✓ Increase 200 mg/day ✓ extended release in 2 divided doses ✓ Regular formulation: 2-4 divided doses
Phenobarbital	30 - 100 daily	300 mg daily (usual effective dose 60 - 200mg)	✓ Titrate in 30 mg increments per 1-2 weeks ✓ As it is sedating, give at bedtime ✓ If morning sedation occurs divide in to 2 doses.
Phenytoin	100mg TID	600 mg daily (usual effective dose ~300mg/day)	✓ Doses up to 200 mg 3 times a day may be necessary. ✓ Consider converting patients from TID doses to BID and once daily doses after good seizure control
Valproic acid	✓ 500mg daily: extended release ✓ 250mg BID: delayed release	3,000 mg (usual effective dose" 1000- 2000mg/day)	✓ Extended release; once ✓ Delayed release: twice daily

When to discontinue AED therapy

(It must be a neurologist decision)

- Overall, about 70% of children and 60% of adults who have their seizures completely controlled with antiepileptic drugs can eventually discontinue therapy.
- The following patient profile yields the greatest chance of remaining seizure free after drug withdrawal:
  - **Complete medical control of seizures for 1- 5 years**
  - **Single seizure type, either focal or generalized**
  - **Normal neurologic examination, including intelligence; and**
  - **Normal EEG.**
- The appropriate seizure free interval is unknown and undoubtedly varies for different forms of epilepsy. However, it seems reasonable to attempt withdrawal of therapy **after 2 years in a patient who meets all of the above criteria**, is motivated to discontinue the medication, and clearly understands the potential risks and benefits.
- In most cases, it is preferable to **reduce the dose of the drug gradually over 2 - 3 months.**
- **Most recurrences occur in the first 3 months after discontinuing therapy**, and patients should be advised to **avoid potentially dangerous situations such as driving or swimming during this period.**

Treatment of refractory Epilepsy

- Approximately **one-third** of patients with epilepsy do not respond to treatment with a single antiepileptic drug, and it becomes necessary to try **a combination of drugs** to control seizures.
- Patients who have focal epilepsy related to an underlying structural lesion or those with multiple seizure types and developmental delay are particularly likely to require multiple drugs.
- There are currently no clear guidelines for rational polypharmacy, although in theory a **combination of drugs with different mechanisms of action** may be most useful.
- In most cases**, the initial combination therapy combines first line drugs** (i.e., carbamazepine, oxcarbazepine, lamotrigine, valproic acid, levetiracetam, and phenytoin).
- If these drugs are unsuccessful, then the addition of other drugs such as topiramate, zonisamide, lacosamide, or tiagabine is indicated.
- Patients with myoclonic seizures resistant to valproic acid may benefit from the addition of clonazepam or clobazam, and those with absence seizures may respond to a combination of valproic acid and ethosuximide**.**
- Treatment options in addition to Combination therapy:
    - Surgery
    - Responsive neuro stimulation
    - Deep brain stimulation
    - Laser thermo ablation
    - Stereotactic radiosurgery

3. Surgical treatment of refractory Epilepsy

- Approximately 20 - 30% of patients with epilepsy continue to have seizures despite efforts to find an effective combination of antiepileptic drugs.
- The most common surgical procedure for patients with **temporal lobe epilepsy** involves resection of the anteromedial temporal lobe **(temporal lobectomy)** or a more limited removal of the underlying hippocampus and amygdala (**amygdalohippocampectomy**).
- **Focal seizures arising from extratemporal regions** may be abolished by a focal neocortical resection with precise removal of an identified lesion (**lesionectomy).**

Special issues related to women & Epilepsy

1. Catamenial Epilepsy

- Some women experience a marked increase in seizure frequency around the time of menses.
- Increase AED dosages during menses.
- Give Natural progestins or intramuscular medroxyprogesterone

2. **Pregnancy**

- Most uncomplicated gestation & normal baby require frequent follow up
- Seizure frequency during pregnancy will remain unchanged in ~50% of women, increase in ~30%,
  and decrease in ~20%.
- Incidence of fetal abnormalities is 5-6% (CVS & MSS), compared to 2—3% in healthy women.
- **Valproic acid is Category X drug**; **Teratogenic** causing Neural tube defects, craniofacial defects, cardiovascular malformations, hypospadias, and limb malformations
- Except Topiramate, newer drugs are safer than valproate
- **Management:**
  - ✓ **Pregnant women should be maintained on effective AED therapy**. Because the potential harm of uncontrolled convulsive seizures on the mother and fetus is considered greater than the teratogenic effects of AED
  - ✓ put on monotherapy at the lowest effective dose, especially during the first trimester
  - ✓ give folate (1-4mg/day)
  - ✓ treat all pregnant mothers with oral vitamin K (20 mg/d, phylloquinone) in the last 2 weeks of pregnancy, and the infant should receive intramuscular vitamin K (1 mg) at birth.

3. **Breast feeding**

- Antiepileptic medications are excreted into breast milk to a variable degree. 5% (valproic acid) to 300% (levetiracetam)
- Mothers with anti-epileptics are encouraged to breast feed unless there is evidence of drug effects on the infant such as lethargy or poor feeding.

4. **Contraception (OCP)**

- AED's such as carbamazepine, phenytoin, phenobarbital, and topiramate can significantly decrease the efficacy of oral contraceptives via enzyme induction and other mechanisms.
- Management: use other forms of contraception

3.7 Respiratory related disorders and infections

3.7.1 Pneumonia (የሳንባ ምች)

- Pneumonia is an acute inflammation of the distal lung-terminal airways, alveolar spaces, and interstisium.
- Common cause of significant morbidity and mortality
- The clinical presentation and the aetiology vary greatly depending on the age of the patient, the infecting organism, the site/s the infection has involved, the immune status of the patient and the place of acquisition of infection.
- can be classified as;
  - ✓ Community acquired (CAP)→ most common than other type of pneumonia
  - ✓ Hospital acquired (HAP)
  - ✓ Ventilator-associated pneumonia (VAP)
  - ✓ Healthcare-associated pneumonia (HCAP)

Pathophysiology

- ❖ Results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens
- ❖ Microorganisms gain access to the lower respiratory tract in several ways;
  - ✓ Aspiration from oropharynx
  - ✓ Inhalation as contaminated droplets
  - ✓ hematogenous spread → rare

Pathology

- Pneumonia evolves through 4 interrelated series of pathologic changes

1. **Alveolar oedema** → The presence of a proteinaceous exudate and bacteria
2. **Red hepatization phase** → Erythrocytes and neutrophils predominate, Bacteria are occasionally seen
3. **Gray hepatization phase** → RBCs are degraded, neutrophils predominate, and bacteria have disappeared, Corresponds with

successful containment of the infection and improvement in gas exchange

4. **Resolution phase** → The debris of neutrophils, bacteria, and fibrin are cleared

Risk factors

- Intrinsic factors- host factors
- Extrinsic factors- exposure to a causative agent, pulmonary irritants, or direct pulmonary injury

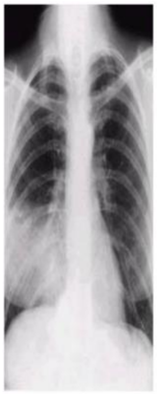
Intrinsic factors	Extrinsic factors- virulence factors
✓ Age ✓ Loss of protective upper air way reflexes ☛ Altered mental status ☛ Endotracheal intubation ✓ Immunosuppression ✓ Dysfunction of local defense mechanisms ☛ Smoking ☛ COPD, bronchiectasis, CF ☛ Tumors ✓ Chronic periodontitis	✓ C. pneumonia produce a cilostatic factor ✓ M. pneumonia can shear off cilia ✓ Influenza virus markedly reduces tracheal mucus velocity ✓ S. pneumonia and N. meningitidis produce proteases that can split secretory IgA

Diagnosis of pneumonia

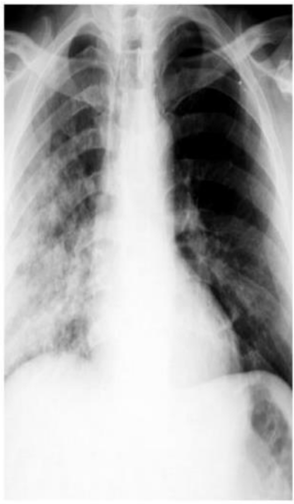
Imaging

Chest X-ray

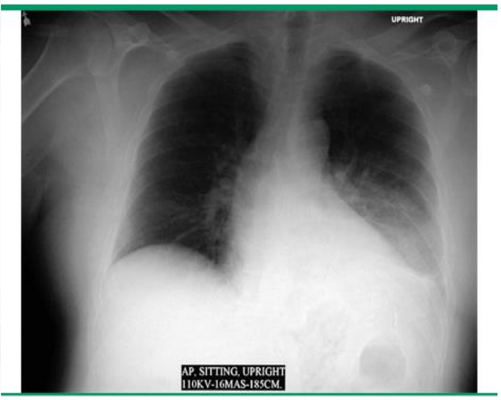
- Typical consolidation
- Classification of pneumonia → Lobar, bronchopneumonia, interstitial pneumonia
- May suggest etiologic diagnosis- eg- pneumatoceles suggest infection with S. aureus
- Risk factors for increased severity- cavitation or multilobar involvement
- Complications- eg- parapneumonic effusion, pneumothorax



Lobar Pneumonia

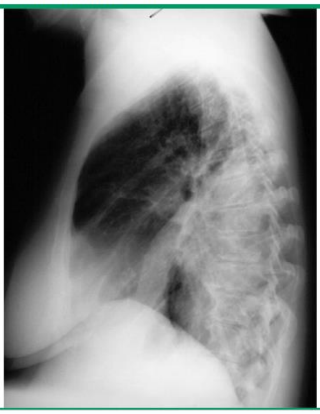


Pneumococcal pneumonia chest radiograph



64-year-old male with insulin-dependent diabetes mellitus. He was admitted with bacteremic pneumococcal pneumonia. Note the left lower lobe opacity.

Pneumonia bulging fissure



Chest radiograph from a 55-year-old female with bacteremic pneumococcal pneumonia. Shows a dense left lower lobe opacity with a bulging fissure.

Etiologic Diagnosis

- Clinical diagnosis with radiologic support usually suffices to diagnose most patients with pneumonia.
- Treatment directed at a specific pathogen is not generally superior to empirical therapy based on clinical and radiologic diagnosis
- **Indications for etiologic diagnosis**
  - ✓ Severe CAP requiring ICU admission
  - ✓ Severe HAP/VAP
  - ✓ Suspicion of pathogens with important public safety implications
    - ☛ M. tuberculosis
    - ☛ Legionella
    - ☛ Influenza virus
    - ☛ Community aquired MRSA (CA-MRSA)
    - ☛ Agents of bioterrorism

❖ CBC

- ✓ **Leucocytosis → Lymphocyte dominant in viral and fungal causes, Neutrophil dominant in bacterial causes**

- ❖ **AFR (ESR and CRP)**
- ❖ Pleural fluid analysis: any parapneumonic effusion should be analyzed.
- ❖ PICT and RBS
- ❖ electrolytes, BUN/Cr, LFTs
- ❖ Gram's stain and culture of sputum
- ❖ Blood culture → about 10 % can be positive.
- ❖ Antigen tests → Urine antigen tests for pneumococcal and legionella, Have high sensitivity and specificity
- ❖ PCR
- ❖ serology

N.B the following three are diagnostic for pneumonia

- **I. Typical CXR findings**
- **II. Leucocytosis**
- **III. Raised ESR**

DDx of pneumonia

1. Acute bronchitis
2. Acute exacerbation of COPD
3. Bronchial asthma
4. Heart failure
5. Pulmonary embolism
6. Radiation pneumonitis

3.7.1.1 Community-Acquired pneumonia (CAP)

- Aetiology — can be caused by bacteria, fungi, viruses, and protozoa
- **"Typical"** bacterial causes
  - ✓ S.pneumonia- the most common cause
  - ✓ H. influenza, *M. catarrhalis* (espec. in COPD'ers)
  - ✓ Pseudomonas
  - ✓ *Klebsiella* & other GNR (espec. in alcoholics & aspirators)
  - ✓ *S. aureus* (espec. post-viral infection)
- **"Atypical"** causes

  - Mycoplasma pneumonia
  - Chlamydia pneumonia
  - Legionella (espec. in elderly, smokers, T immunity)
  - Influenza viruses
  - Adenoviruses
  - Respiratory syncytial virus
- **No organism** identified in 40—60% cases

Clinical manifestations

“Typical”:

- acute onset of **fever**
- **cough** with purulent sputum
- **chest pain**
- dyspnea
- **Increased or decreased tactile fremitus and dull percussion note**
- **Crackles, BBS, and/or pleural friction rub**
- consolidation on CXR

“Atypical”: (originally described as culture negative): tends to present with

- insidious onset of dry cough
- extra pulmonary symptoms (N/V, diarrhoea, headache, myalgias, sore throat)
- patchy interstitial pattern on CXR
- elevated transaminases & low serum Na with *Legionella.*

N.B

- Signs, symptoms & imaging do *not* reliably distinguish between “typical” (*S. pneumo*, *H. flu*) and “atypical” (*Mycoplasma*, *Chlamydia, Legionella,* viral)
- The clinical presentation may not be so obvious in the elderly, who may initially display new-onset or worsening confusion
- Severely ill patients may have septic shock and evidence of organ failure

Management of CAP

CAP outpatient without comorbidities or other risk

First line

- ✓ Amoxicillin 1g, PO, TID, for 5 - 7 days

Second line

- ✓ Azithromycin, 500mg po daily for 3 days (500mg P.O., first day then 250mg P.O. daily, for 4d) or
- ✓ Clarithromycin, 500mg P.O. BID for 5-7 days Or
- ✓ Doxycycline, 100mg P.O., BID for 7-10 days.

CAP outpatient + with risk or comorbidities (*chronic heart, lung, kidney or liver disease, DM, alcoholism, malignancy, asplenia), elderly, recent antibiotic use (within 3 months)*

First line

- ✓ Augmentin (Amoxicillin-clavulanate), 625mg P.O., TID for 5-7days
  - ☛ Or 1g (875 mg/125 mg), PO, BID or
  - ☛ 2g/125 mg, PO, BID

  plus
- ✓ Azithromycin, 500mg po daily for 3 days (500mg P.O., first day then 250mg P.O., for 4d.) or
- ✓ Clarithromycin, 500mg P.O. BID for 5-7 days OR
- ✓ Doxycycline, 100mg P.O., BID for 7-10 days.

Second line

- ✓ Cefuroxime 250-500mg, po, bid for 5-10 days Plus
- ✓ Azithromycin, 500mg po daily for 3 days (500mg P.O., first day then 250mg P.O., for 4d.) OR
- ✓ Clarithromycin, 500mg P.O. BID for 5-7 days

Prevention

- ➢ Influenza vaccination
- ➢ Pneumococcal vaccination is critical for at risk patients
  - ✓ may be given for ≥65 years old patients and others with risk factors (eg, chronic heart, lung, and liver disease, immunocompromised, and impaired splenic function)
- ➢ Smoking cessation should be encouraged during the initial visit

- Other infection prevention measures

3.7.1.2 Hospital-acquired pneumonia /HAP/ (Nosocomial Pneumonias)

- **Hospital-acquired (or nosocomial) pneumonia (HAP)** is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.
- **Ventilator-associated pneumonia (VAP)** is a type of HAP that develops more than 48 to 72 hours after endotracheal intubation.
- **Healthcare-associated pneumonia (HCAP)** is used to classify patients with multidrug resistance (MDR) pathogen risk. **This is no more used currently.** Currently HCAP is **classified under CAP.** Specific risk factors for resistance include recent antimicrobial use, comorbidities, functional status, and severity of illness.

Investigation and Diagnosis

- Three key criteria are required for the diagnosis of HAP and VAP
  1. A new or progressive lung infiltrate of infectious origin
  2. Clinical presentations (after 48 hours of admission for HAP and after 48 hours of intubation for VAP) ensuring an infection (fever, purulent sputum, leucocytosis, decline in oxygenation)
  3. A positive pathogen identified on microbiologic respiratory samples. Despite the controversies on the type of samples taken and the analysis method, microbiologic cultures are absolutely required for guiding the empiric therapy in HAP/VAP and has to be taken prior to the first antibiotic dose administration.

Management

- The antibiotic choice should depend on the epidemiology and susceptibility of local pathogens.
- Empiric treatment should include antimicrobials effective against resistant gram-positive and gram-negative organisms particularly S.aureus and P.aeruginosa.
- The following are possible combinations: Empiric treatment for commonly suspected etiologies of HAP.

First line

- ✓ Vancomycin 1g I.V. BID for 10-14 days (particularly in the ICU setup and in ventilator associated pneumonia)

PLUS

- ✓ Ceftazidime, 2gm I.V. TID for 10-14days Or
- ✓ Cefepime, 2 g, IV, TID

2nd line

- ✓ Ceftriaxone, 1-2g I.V. OR I.M. BID for 7 days.
  PLUS
- ✓ Gentamicin, 5 to 7 mg/kg IV daily for 7 days. OR
- ✓ Ciprofloxacin, 400 mg IV TID for 7 days. (IV can be changed to 750 mg, PO, BID once patient is stable and able to take PO)

3rd line → reserved for microbiologic data proven resistance for 1st and 2nd line options

- Alternative for vancomycin
  - ☛ Meropenem, 1gm IV (infused slowly over 30min) TID OR
  - ☛ Imipenem-cilastatin, 500mg IV (infused slowly over 1hour) QID
- Alternative for gentamycin
  - ☛ Amikacin 15 to 20 mg/kg IV daily

If methicillin-resistant (MRSA) suspected

- ✓ Vancomycin, 1 g I.V. BID should be added to the existing empric regimen

N.B. All empiric regimens are subject to modification on the arrival of microbiologic results and other evidences. De-escalation to narrow spectrum antibiotics and oral regimens are always encouraged in the appropriate circumstances.

3.7.1.3 Aspiration pneumonia:

- Aspiration pneumonia is a pulmonary reaction resulting from the abnormal entry of fluid, particulate exogenous substances, or endogenous secretions into the lower airways.
- Most cases arise following gross "aspiration" of microorganisms from the oral cavity or nasopharynx.
- If untreated, pneumonia may complicate to lung abscess, necrotizing pneumonia, or empyema secondary to a Broncho pleural fistula.

Conditions that predispose to aspiration

- ✓ Altered consciousness due to alcoholism/drug overdose, seizures/head trauma, general anaesthesia
- ✓ Dysphagia due to various reasons (e.g., stricture, neoplasm, xerostomia, etc)
- ✓ Neurologic disorder (e.g. cerebrovascular accident)
- ✓ Mechanical disruption of the usual defence barriers (e.g. intubation)
- ✓ Disorders of the GIT
- ✓ Other: Protracted vomiting, pharyngeal anaesthesia, general debility, recumbent position, glottic insufficiency etc.

- Aspiration pneumonia is caused by a compromise in the usual defences that protect the lower airways and then introduction of inoculum deleterious to the lower airways.
- The inoculum will either be directly toxic or stimulate the inflammatory process or obstruct the airway.
- **The three syndromes of aspiration are:**
    1. **chemical pneumonitis**
    2. **bacterial infection and**
    3. **airway obstruction.**

Clinical features

- ✓ Mostly indolent course over several days or weeks
- Fever, cough, purulent sputum, and dyspnea
- Systemic disease symptoms: night sweets, weight loss, anemia
- Hemoptysis or pleurisy
- Copious putrid or malodorous sputum is typical for anaerobic infection
- Absence of chills or rigors

Investigations and diagnosis

- ✓ Chest X-ray
- ✓ gram stain and culture
- ✓ Pleural fluid analysis and blood cultures

Management of aspiration pneumonia

- antibiotics are indicated only in documented respiratory tract infection (clinical, radiologic and microbiologic confirmation required)

Community onset Aspiration Pneumonia *Mixed infection*

(anaerobes and facultative anaerobes like oral streptococci)

Mild to moderate

First line

- ✓ amoxicillin clavulanate 625mg PO TID or (875 mg/125 mg BID, or 2,000 mg/125 mg BID) x 7 days or
- ✓ ampicillin-sulbactam 1.5 - 3 g IV QID

Second line

- ✓ amoxicillin 500 mg PO TID x 7 days or
- ✓ penicillin G 1 - 2 million units, IV, QID x 7 days
  PLUS
- ✓ Metronidazole, 500 mg, PO, TID x 7 days

- ➢ Clindamycin 600 mg IV TID is appropriate for penicillin-allergic patients.

Severe

First line

- ✓ Ampicillin sulbactam 1.5 - 3 g IV QID x 7 days

Second line

- ✓ ceftriaxone 1g IV BID (2 g IV daily) or
- ✓ cefotaxime 1 - 2 g IV TID
  PLUS
- ✓ metronidazole 500 mg, IV, TID x 7 days

Hospital onset Aspiration Pneumonia

(aerobic bacteria, especially Gram -ve bacilli and S.aureus, are more likely than the anaerobes)

First line

- ✓ piperacillin tazobactam 2g IV TID x 7 days

Second line

- ✓ Ceftazidime 2g IV TID to QID or
- ✓ cefepime 2 g IV BID to TID or
- ✓ Meropenem, 1gm IV (infused slowly over 30min) TID

- ➢ If risk factor for MRSA (e.g MRSA colonization), add vancomycin; if MRSA is not detected in a culture, discontinue it.

3.7.1.4 Severe pneumonia

- Assessment of severity is important to decide the place of care of the patient
- Patients with severe pneumonia should be hospitalized
- There are currently two sets of criteria
  1. CURB-65
  2. The pneumonia severity index (PSI)

- ➢ CURB-65 — easy and commonly used scoring system which stands for:

- ✓ Confusion* (1 point)
- ✓ Urea >20 mg/dL (7 mmol/L) ** (1 point)
- ✓ RR $\geq$30 bpm (1 point)
- ✓ SBP (<90 mmHg) or DBP ($\leq$60 mmHg) (1 point)
- ✓ Age $\geq$65 years (1 point)

**Defined as an Abbreviated Mental Test Score $\leq$8 or new disorientation to person, place, or time.*
***Urea is blood urea nitrogen [BUN], expressed in mg/dL or serum urea concentration, expressed in mmol/L.*

0 to 1 point:	Low severity (risk of death <3%)	Outpatient treatment, PO antibiotic
2 points:	Moderate severity (risk of death 9%)	
3 to 5 points:	High severity (risk of death 15 to 40%)	In patient, IV antibiotic immediately after culture

ICU admission criteria

- CURB-65 predictive rules however, are not used as criteria for high-level (ICU) care and treatment intensification.
- The Infectious Disease Society of America (IDSA) recommends either **1 major criterion** or ≥ **3 minor criteria for ICU admission criteria.**

- **Major criteria** (If one)
  - Septic shock with need for vasopressors
  - Respiratory failure requiring mechanical ventilation

- **Minor criteria** (≥ 3)
  - RR ≥ 30 bpm
  - Hypothermia (core temperature, <36C)
  - Hypotension requiring aggressive fluid resuscitation
  - Multilobar infiltrates
  - Confusion/disorientation
  - Uraemia (BUN level ≥20 mg/dl)
  - Leukopenia /infection related only/ (WBC, <4,000 cells/ml)
  - Thrombocytopenia (platelet count, <100,000/ml)
  - PaO2/FI O2 ratio ≤250

Management of Severe Pneumonia (Community acquired hospitalized patients)

- Bed rest
- Frequent monitoring of V/S in order to detect complications early and to monitor response to therapy.
- Give attention to fluid and nutritional replacements.
- Administer Oxygen via nasal prongs or face mask
- The Antibiotic choice should be aimed at the most likely causative agent.
- Empiric treatment for pneumonia due to common organisms:

First line

- ✓ Ceftriaxone 1g, IV, BID for 5 to 7 days **OR**
- ✓ cefotaxime 500mg, IV, QID for 5 to 7 days
  PLUS
- ✓ Azithromycin, 500mg po daily for 3 days **OR**

- ✓ Clarithromycin, 500mg P.O. BID for 5-7 days

Second line

- ✓ Augmentin 625mg P.O., TID for 5-7days
  plus
- ✓ Azithromycin, 500mg po daily for 3 days OR
- ✓ Clarithromycin, 500mg P.O. BID for 5-7 days

N.B. In a situation of beta lactam allergy, respiratory fluoroquinolones (moxifloxacin or levofloxacin) can be used. As these medicines are second line medicines for Tuberculosis, they should only be used when it is absolutely important.

3.7.1.5 Empyema and Complicated Parapneumonic Effusions

Uncomplicated parapneumonic effusion	**Complicated parapneumonic effusion**	**Empyema**
An exudative effusion with either of the following characteristics ➢ Small size (1cm in lateral decubitus position), non-loculated: gram stain, culture, glucose level of pleural fluid being unknown **OR** ➢ Moderate size (>1cm but <1/2 of the hemithorax), non loculated: **gram stain and culture confirmed to be negative** and pleural fluid glucose >60mg/dl.	An exudative effusion with **negative pleural fluid culture and gram stain** along with the presence of one of the following: ➢ Large non-loculated (free flowing) pleural effusion involving >1/2 of the hemithorax ➢ Loculated pleural effusion ➢ Pleural effusion with thickened pleura ➢ Pleural fluid glucose <60mg/dl	Refers to invasion of the pleural space by a significant number of bacteria. The presence of either of the following defines empyema ➢ Gross pus **OR** ➢ Positive gram stain or positive culture from pleural fluid.

Clinical features

- ➢ The clinical features of parapneumonic effusion are similar to pneumonia. Pleuritic chest pain and prolonged fever are more common in patients who develop complicated parapneumonic effusion or empyema.
- ➢ Physical examination: signs of pleural effusion (dullness, decreased or absent air entry, decreased tactile fremitus) will be present.

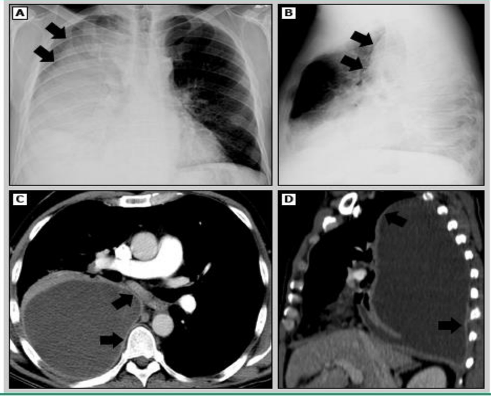
Investigations

→ In addition to the investigations mentioned for pneumonia

- ❖ Pleural fluid cell count with differential, LDH, Protein, glucose, gram stain, culture and AFB

- ❖ Chest ultrasound → useful for suspected loculated pleural effusion
- ❖ Chest CT scans → if CXR and ultrasound are not conclusive

Empyema due to *Staphylococcus aureus*



Posterior (A) and lateral (B) chest radiographs show large loculated right pleural effusion (arrows). Cross-sectional (C) contrast-enhanced multidetector computed tomography (CT) image and sagittal reformation (D) demonstrate the extent of the loculated effusion, pleural thickening, and enhancement (arrows). The patient was a 44-year-old man and an intravenous drug user. He had no radiologic evidence of the septic embolism.

Treatment

Table: Management of parapneumonic effusion and empyema

Types	Treatment
Uncomplicated parapneumonic effusion	Antibiotics alone, no drainage
Complicated parapneumonic effusion	Chest tube drainage* (also called tube thoracostomy) + Antibiotics
Empyema	Urgent chest tube drainage* (tube thoracostomy) + antibiotics
**If clinically & radiologically improve and drainage rate fall below <50 ml/day for 2 to 3 days, remove chest tube* **If no improvement: assess antibiotic coverage (re-culturing, reviewing anaerobic and MDR pathogens coverage) and evaluate for the presence undrained loculated pockets.*	

Surgery (beyond chest tube drainage):

- ➢ Options: thoracoscopic drainage, standard thoracotomy, or open drainage
- ➢ Indications: Multiple loculations or lack of improvement with chest tube drainage

Empiric antibiotic treatment

- ☛ All patients with parapneumonic effusion or empyema need an antibiotic therapy. Antibiotics should be administered promptly (not delayed for sampling or drainage procedures) for better outcome.

- ☛ Anaerobic coverage should be maintained irrespective of culture results as anaerobic organisms are difficult to grow.
- ☛ The duration of antibiotic should be decided on patient by patient basis; mainly based on clinical response. Complete radiologic resolution might take months.

Table: Empiric therapy for adult parapneumonic effusion or empyema patients

Types of effusion		First line	Second line	Duration
Community Acquired	Uncomplicated parapneumonic Effusion	✓ ceftriaxone or ✓ cefotaxime	✓ amoxicillin-clavulanate or ✓ ampicillin-sulbactam if allergy: ✓ metronidazole plus ✓ levofloxacin or ✓ ciprofloxacin	1-2 wks
	Complicated parapneumonic Effusion	✓ ceftriaxone or ✓ cefotaxime plus ✓ metronidazole		2-3 wks
	Empyema			4-6 wks
Hospital Acquired	Uncomplicated parapneumonic Effusion	✓ vancomycin plus ✓ ceftazidime or ✓ cefepime plus ✓ metronidazole	✓ vancomycin plus ✓ piperacillin-tazobactam or ✓ ticarcillin-clavulanate or ✓ Meropenem/imipenem If series penicillin-allergic: ✓ vancomycin plus ✓ metronidazole plus ✓ ciprofloxacin	1-2 wks
	Complicated parapneumonic Effusion			2-3 wks
	Empyema			4-6 wks

Follow up

- ❖ Uncomplicated parapneumonic effusion
  - ✓ repeat imaging after 48-72 hour of antibiotic treatment initiation for any completion
- ❖ Complicated PE and empyema
  - ✓ has microbiologic (easy to grow) or biochemical evidence of infection, at risk of poor outcome (may need repeated procedure or surgery or hospitalization)

  - ✓ repeat CT after 48-72 hour of antibiotic treatment initiation for response
- ❖ empyema
  - ✓ If possible, discharge with 2 weeks follow up schedule
  - ✓ If failed response:
    - assess antibiotic coverage (re-culturing directly from the pleural space or undrained locule but not from tube or catheter drain) and
    - adjust antibiotic coverage for anaerobes and MDR pathogens and
    - assess for a need for additional drainage

3.7.2 Acute tonsillopharyngitis (የቶንሲል በሽታ ፣ የአንቃር እና ጉሮሮ ብግነት)

- Acute infection of the lymphoepithelial tissue of the faucial isthmus, the palatine tonsil, pharyngeal (adenoid) tonsil, lingual and tubal tonsil is known as tonsillitis.
- The commonest causes are viral, followed by less likely GAS (Group A beta-hemolytic Streptococci), Staphylococci, Streptococcus Pneumoniae (Diplococcus pneumoniae) and Haemophilus.

Etiology		**Causative organisms**	
Bacteria	Viruses	**Based on age**	Based on findings
➢ S. pyogenes (GABHS) ➢ C. diphtheriae ➢ N. gonorrhoeae	➢ Rhinovirus ➢ EBV ➢ Adenovirus ➢ Influenza A, B ➢ Coxsackie A ➢ Parainfluenza	➢ < 3 years ≅ 100 % viral ➢ 5-15 years 15-30 % GABHS ➢ Adult 10 % GABHS	**Exudates and Lymphadenopathy** ➢ GABHS ➢ EBV ➢ Adenovirus ➢ HIV ➢ Candida albicans ➢ Francisella tularensis

4.1.1.1 Streptococci tonsilloPharyngitis

- Infection is acquired through contact with another individual carrying the organism.

- **Respiratory droplets are the usual mechanism of spread**, although other routes, including food-borne outbreaks, have been well described.
- Spread more in crowded areas (KG, school, army.)

- Although seen in patients of all ages, GAS pharyngitis is one of the **most common bacterial infections of childhood**
  - Accounts for 20 - 40% of all cases of exudative pharyngitis in children
  - **it is rare among those under the age of 3.**
  - Most common among 5-15 age group declines in late adolescence and adulthood.
- More frequent among lower socio-economic classes
- Most common during winter and spring

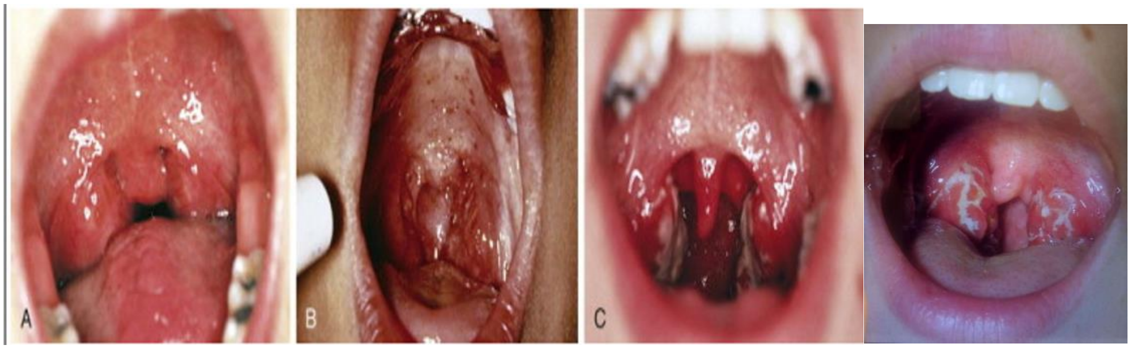
Clinical manifestations

- Younger children may manifest streptococcal infection with a syndrome of fever, malaise, and lymphadenopathy without exudative pharyngitis.
- The incubation period is 1 - 4 days.
- Symptoms include;
  - **Sore throat**
  - **fever and chills** (**> 38 °C**)
  - malaise, and
  - sometimes abdominal complaints and vomiting, particularly in children.
- Both **symptoms and signs** are quite variable**, ranging from mild throat discomfort** with minimal physical findings **to high fever and severe sore throat associated with**;
  - **Intense erythema and swelling of the pharyngeal mucosa**
  - **Purulent exudate over the posterior pharyngeal wall and**
  - **Tonsillar pillars.**
- Pain on swallowing that radiates to the ear.
- Opening the mouth is often difficult and painful if it is complicated.
- Usually associated with systemic symptoms like Headache and marked feeling of malaise, chills, rigor, Nausea, vomiting
- **Absence of coughing**
- Absence of nose drip
- Absence of hoarseness
- Streptococcal infection is an unlikely cause when symptoms and signs suggestive of viral infection are prominent (conjunctivitis, coryza, cough, hoarseness, or discrete ulcerative lesions of the buccal or pharyngeal mucosa).

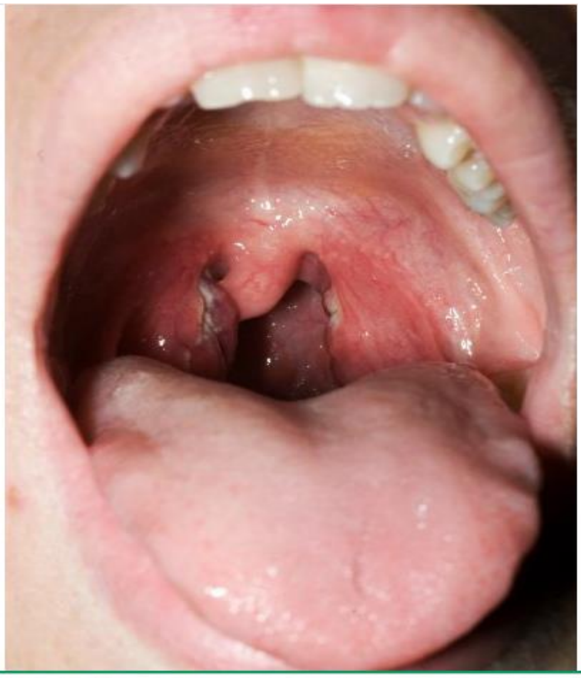
Signs

- **Tonsillar swelling with hyperemia / exudates (**Inflamed and reddened enlarged tonsils)

  - **Exudates are apparent in bacterial tonsillitis**, hyperemia only may be from viral causes (but this differentiation is not stereotypical)
- **Tender cervical lymphadenopathy**
  - Enlarged, tender anterior cervical lymph nodes commonly accompany exudative pharyngitis
- Soft palate petechia
- Other features that support the diagnosis include palatal petechiae, a scarlatiniform rash, and a strawberry tongue (eg, Scarlet fever).

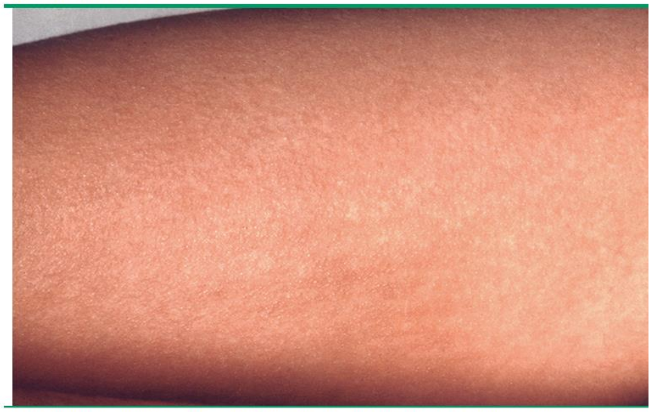


Pictures; Tonsillopharyngitis



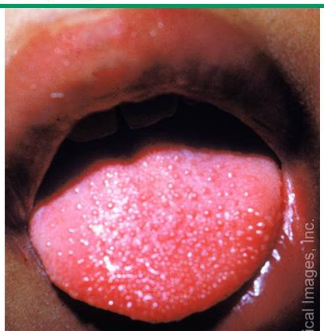
This patient with streptococcal pharyngitis has prominent bilateral tonsillar exudate without peritonsillar swelling, and scattered tonsillar petechiae.

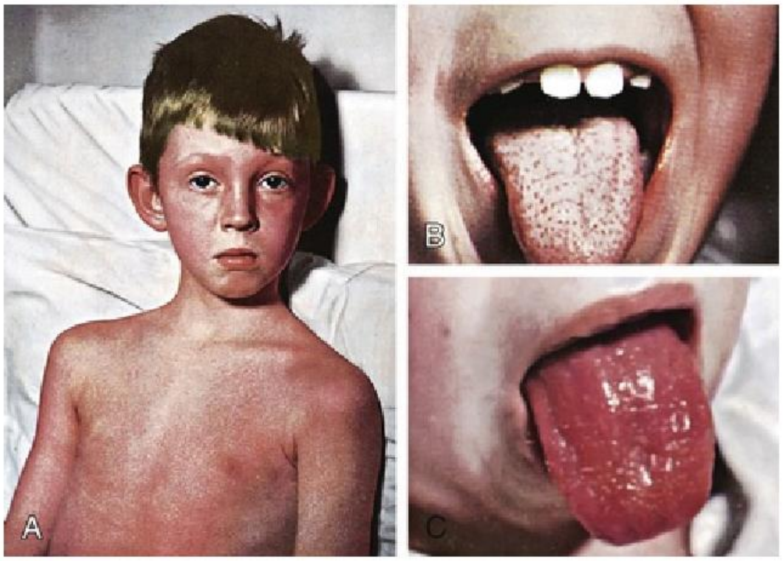
Scarlatiniform rash



Scarlet fever rash on the volar surface of the forearm. The scarlet fever rash first appears as tiny red bumps on t chest and abdomen that may spread all over the body. Looking like a sunburn, it feels like a rough piece of sandpaper, and lasts about two to five days.

Strawberry tongue





10.1 Scarlet fever. A, Punctate, erythematous rash (2nd day). B, White strawberry

Diagnostic approach

Mc Isaac Scoring

Clinical Findings	Score
I. Fever > 38^0C	1
II. Absence of coughing	1
III. Tonsillar hypertrophy or exudates	1 (if< 6 years give 0)
IV. Swollen and tender cervical LN	1
V. Age 3 — 14	1
☛ Age > 45	-1

Total score	Probability of strep	**Suggestions**
0 & 1 points	< 10%	No culture, no antibiotics
2 point	11-17%	Take culture (or antigen test), order antibiotics only if GABHS +ve
3 points	28-35%	
4 & 5 points	52%	➢ Take culture (or antigen test), order antibiotics only if GABHS +ve ➢ **If the c/f is severe, start antibiotics without testing**

4.1.1.2 Viral tonsillitis/pharyngitis

- Viral tonsilo-pharyngitis is most common.
- Rhinovirus (most common).
- Symptoms usually last for 3-5 days.
- Having additional rhinitis, hoarseness, conjunctivitis and cough
- Pharyngitis is accompanied by conjunctivitis in adenovirus infections
- Oral vesicles, ulcers point to viruses

Complication of Tonsillitis due to Streptococci

- Can be classified as Suppurative and Nonsuppurative or **local and systemic**
- **Suppurative complications** result from the **spread of infection** from the pharyngeal mucosa to deeper tissues by direct extension or by the hematogenous or lymphatic route
    - **Suppurative complications** of streptococcal pharyngitis have become **uncommon** with the widespread use of antibiotics for most symptomatic cases.
- **Nonsuppurative complications** are thought to result from **immune responses** to streptococcal infection.
    - **Penicillin treatment of streptococcal pharyngitis reduces the likelihood of ARF but not that of PSGN.**

Suppurative VS Nonsuppurative	local VS systemic
Suppurative complications ➢ peritonsillar or retropharyngeal abscess ○ These local complications should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance. ➢ **cervical lymphadenitis** ➢ **sinusitis** ➢ **otitis media** ➢ **mastoiditis** ➢ **meningitis** ➢ bacteremia ➢ endocarditis and ➢ pneumonia. ➢ **Recurrent** tonsillitis/pharyngitis	**Local complications** ✓ peritonsillar abscess ✓ parapharyngeal abscess ✓ retropharyngeal abscess **Systemic complication** ✓ Septicemia ✓ ARF ✓ PSGN
Nonsuppurative complications ➢ **ARF (Acute rheumatic fever)** ○ Due to cross reaction to type 5 M-protein ➢ **PSGN (Post streptococcal glomerulonephritis)** ○ PSGN is an acute glomerulonephritis (AGN) due to nephritogenic strains ➢ Poststreptococcal **reactive arthritis** (PSRA) ➢ Scarlet fever ➢ Streptococcal toxic shock syndrome	

Investigation

- **In our set up it is usually a clinical diagnosis**. But ''Harrison'' didn't recommend clinical diagnosis
    - *''Because of the range of clinical presentations of streptococcal pharyngitis and the large number of other agents that can produce the same clinical picture, diagnosis of streptococcal pharyngitis on clinical grounds alone is not reliable''.*
- **Rapid diagnostic kit** (for latex agglutination or enzyme immunoassay of swab specimens)
    - ✓ is a useful adjunct to throat culture.
    - ✓ >95% specific. but, less sensitive (55—90%).
        - Thus, a positive result can be relied upon for definitive diagnosis and eliminates the need for throat culture
        - A negative result should be confirmed by throat culture.
- Throat swab culture → **Gold standard**
    - It is hard to differentiate viral and bacterial cause based on symptom and sign alone. Thus, Throat swab is done to r/o bacterial cause
    - Culture of a throat specimen that is properly collected (i.e., by vigorous rubbing of a sterile swab over both tonsillar pillars) and properly processed is the most sensitive and specific means of definitive diagnosis.
    - Not required usually. **Needed only when suspicion is high and rapid strep throat swab is negative.**
    - Pathogens looked for
        - GAS
        - C. diphteriae (rare)
        - N. gonorrhoeae (rare)
- ASO
    - ✓ May remain +ve for 1 year
- Peripheral smear → BF (to r/o malaria in endemic area)
- CBC and ESR

Treatment of GABHS

- **The goal of antibiotic therapy** for streptococcal pharyngitis is multifold and includes:
    - Reducing symptom severity and duration
    - Prevention of acute complications, such as otitis media, peritonsillar abscesses, or other invasive infections
    - Prevention of delayed complications or immune sequelae, particularly acute rheumatic fever
        - **The primary benefit of treatment is the prevention of acute rheumatic fever, which is almost completely successful if antibiotic treatment is instituted within 9 days of illness.**
    - Prevention of spread to others

4.1.2 Adjunctive treatment

- **Supportive care** (rest, adequate fluid intake, avoidance of respiratory irritants, soft diet) to all patients and
- **NSAIDs or PCM** for fever or pain control.

4.1.3 Antibiotics in Tonsillitis/pharyngitis due to GABHS

5. Antibiotic treatment is the mainstay of care.

Table; Treatment of Tonsillopharyngitis due to group A *Streptococcus*

	Antibiotic class	Drug (select one)	**Dosing in adults**	**Dosing in pediatrics**
First line	**Penicillin's**[@]	**Penicillin V**	500 mg, PO, BID to TID for 10 days	If ≤27 kg: 250 mg, PO, BID to TID, for 10 days If >27 kg: the same as adult dose
		Amoxicillin	500 mg, PO, BID for 10 days	50 mg/kg/day (maxi;1g/day), PO, BID or TID for 10 days
		Penicillin G benzathine	1.2 million units, IM, stat	<27kg: 600,000 units, IM, stat >27 kg: the same as adult dose
Alternatives (used if there is allergy to penicillins. See foot note)	**Cephalosporins** [Δ]	**Cephalexin**	500 mg, PO, BID for 10 days	40 mg/kg/day, PO, BID for 10 days (max; 500 mg/dose)
		Cefuroxime	250 mg, PO, BID for 10 days	10 mg/kg/dose, PO, BID, for 10 days (max; 250 mg/dose)
		Cefixime	400 mg, PO, daily to BID, for ≥ 10 days	Children ≥6 months and ≤45 kg: ✓ 8 mg/kg/day, PO, daily to BID for ≥10 days (max: 400 mg/day) Children >45 kg or >12 years: ✓ The same as Adult dose
		Cefpodoxime	100 mg, PO, BID for 5 - 10 days	5 mg/kg/dose, PO, BID (max; 100 mg/dose), for 5 to 10 days
		Cefdinir	300 mg, PO, BID for 5 - 10 days or 600 mg, PO, daily for 10 days	7 mg/kg/dose, PO, BID, for 5 to 10 days or 14 mg/kg/dose, daily for 10 days (max; 600 mg/day)
	Macrolides[#]	Azithromycin	500 mg, PO, daily for 3 days or 500 mg, PO, on day 1 followed by 250 mg on days 2 through 5	12 mg/kg (max; 500 mg/dose), PO, daily for 3 days or 12 mg/kg, on day 1 followed by 6 mg/kg/dose (max;250 mg/dose), PO, daily on days 2 through 5
		Clarithromycin	250 mg, PO, BID, for 10 days	7.5 mg/kg/dose (max; 250 mg per dose), PO, BID for 10 days
		Erythromycin	250 mg, PO, QID, for 10 days	10 mg/kg/dose, PO, QID (maxi; 250 mg per dose) for 10 days

	Lincosamides*	Clindamycin	300 mg, PO, TID for 10 days	7 mg/kg/dose (max;300 mg per dose), PO, TID, for 10 days

@ **Penicillin's** (oral penicillin, oral amoxicillin, or single-dose IM benzathine penicillin) are options for patients with a history of acute rheumatic fever (who are high risk for cardiac complications compared with those without this history)

- ➢ IM penicillin appears to be more effective than oral penicillin at eradication of GAS from the oropharynx and has been most well studied for the prevention of acute rheumatic fever

Δ **Cephalosporins** are Potential alternatives in cases of penicillin allergy

- if the nature of the allergy is mild reactions to penicillin, non-IgE-mediated reactions to penicillin (e.g. **maculopapular rash** beginning days into therapy) **a 1st generation cephalosporin** such as **cephalexin**
- For patients with mild, possibly IgE-mediated reactions (e.g. **urticaria or angioedema but NOT anaphylaxis**), they use **a 2nd- or 3rd-generation cephalosporin**, such as **cefixime, ceftriaxone, cefuroxime, cefdinir, or cefpodoxime.**

# **Macrolides** are alternatives for patients with immediate hypersensitivity reaction (**anaphylaxis**) or another **potentially life-threatening manifestation (e.g., severe rash and fever**). or other IgE-mediated reactions, who cannot tolerate cephalosporins

- In areas with resistance rates exceeding 5—10%, macrolides should be avoided unless results of susceptibility testing are known.

* **Lincosamides** (e.g. Clindamycin) are alternative **when macrolide resistance is a concern** and penicillin's and cephalosporins cannot be tolerated.

Antibiotics NOT to be used for GABHS due to the high prevalence of resistance include;

- ✓ Tetracycline
- ✓ Sulphonamides (e.g. Co-trimoxazole)
- ✓ fluoroquinolones (e.g. Aminoglycosides)
- ✓ Chloramphenicol

- ➢ Follow-up culture after treatment is no longer routinely recommended but may be warranted in selected cases, such as;
  - Those involving patients or families with frequent streptococcal infections or
  - Those occurring in situations in which the risk of ARF is thought to be high (e.g., when cases of ARF have recently been reported in the community).

Bacteriologic treatment failure and asymptomatic carrier state

- up to 20% of individuals in certain populations may have asymptomatic pharyngeal colonization with GAS.
- There are no definitive guidelines for management of these asymptomatic carriers or of asymptomatic patients who still have a positive throat culture after a full course of treatment for symptomatic pharyngitis.

- A reasonable course of action is to **give a single 10-day course of penicillin for symptomatic pharyngitis** and, if positive cultures persist, **not to re-treat unless symptoms recur**.
- The risk both of developing ARF and of transmitting infection to others is substantially lower among asymptomatic carriers than among individuals with symptomatic pharyngitis.
- Therefore, overly aggressive attempts to eradicate carriage probably are not justified under most circumstances. An exception is the situation in which an asymptomatic carrier is a potential source of infection to others. Outbreaks of foodborne infection and nosocomial puerperal infection have been traced to asymptomatic carriers who may harbor the organisms in the throat, vagina, or anus or on the skin.

Treatment of Asymptomatic Pharyngeal Colonization with GAS

- When a carrier is transmitting infection to others, attempts to eradicate carriage are warranted.
- GAS (Group A streptococci) chronic carrier, treatment:
  - **Amoxicillin clavulanate** 875/125 mg (1g), PO, BID for 10 days
    - For pediatrics; Amoxicillin clavulanate syrup (400mg/5mL), 40 mg/kg/day, PO, TID, for 10 days (max: 2g/day)
- Even though limited data, Regimens reported to have efficacy superior to that of penicillin alone for eradication of carriage include;
  - a **first-generation cephalosporin** such as cephalexin (30 mg/kg; 500 mg max), PO, BID for 10 days or
  - **clindamycin, 300mg** (for children; 7 mg/kg; 300 mg max) PO, TID for 10 days.
  - A 10-day course of vancomycin (250 mg, PO, QID) and rifampin (600 mg, PO, BID) has eradicated rectal colonization.

Persistent or recurrent symptoms

- For patients who have persistent or recurrent symptoms consistent with GAS pharyngitis after completing a course of antibiotic therapy, repeat testing for GAS.
  - Culturing for GAS when patients are between episodes may help distinguish chronic carriage from active infection.
  - A positive culture in an asymptomatic patient suggests that the patient is a carrier and that symptoms are due to an alternate cause
- Because chronic GAS carriage can occur after antibiotic therapy, avoid testing in patients whose symptoms are highly consistent with viral pharyngitis (e.g. sore throat accompanied by cough, conjunctivitis, or rhinorrhea) or other etiology.

Cause of recurrence or persistence	Actions to be taken and management

	➢ **Repeat a 10-day course of antibiotic** treatment for patients with persistent or recurrent streptococcal pharyngitis. ➢ The selection of an antibiotic varies based on cause
Nonadherence	✚ treat with intramuscular penicillin. ○ Injections of penicillin G benzathine provide bactericidal levels against GAS for 21 to 28 days. ✚ For those who are allergic or who cannot otherwise tolerate penicillin, individualize antibiotic selection based on the patient's preferences and reasons for nonadherence
Recurrent infection, which refers to new infection with the initial infecting strain or a new strain ➢ Suspected when clusters of GAS infections are occurring within the patient's household, school, workplace, or other close-contact setting. ➢ Symptoms associated with recurrent infection with the same serotype may be milder than with the initial infection.	✚ select an antibiotic that has greater beta-lactamase stability than the one used for the initial treatment course. Examples; ○ **if penicillin was used for initial treatment**, use either **amoxicillin-clavulanate (875mg/125mg, PO, BID)** or a **first-generation cephalosporin** ○ **if a first-generation cephalosporin was used**, select **a 2nd or 3rd-generation cephalosporin** ✚ For patients with **multiple recurrences** of GAS pharyngitis, **treat with an antibiotic** from a class **that has not been used previously**, such as clindamycin. ✚ For patients with **frequent, severe episodes** of GAS pharyngitis **that recur despite appropriate antibiotic** treatment, **consider tonsillectomy.**
Persistent infection (a.k.a treatment failure) ➢ rare but most often occurs in children, particularly those under age 5. ➢ Selection of an antibiotic to which there is potential GAS resistance, such as a macrolide or clindamycin, increases the likelihood of treatment failure	
Infection with a different pathogen superimposed on chronic GAS carriage	Identify and treat
Presence of a **suppurative complication**	
Alternative initial diagnosis	

Peritonsillar abscess

- Inadequately treated acute or chronic tonsillitis can spread to the surrounding tissue and form abscess called peritonsillar abscess

Clinical features

- Severe pain such that the patient often refuses to eat
- The head is held over to the diseased side, and rapid head movements are avoided.

- The patient has sialorrhea and oral fetor
- Swelling of the regional lymph nodes
- Fever with high temperatures of 39°C to 40°C and the general condition deteriorates rapidly.
- Redness, and protrusion of the tonsil, the faucial arch, the palate and the uvula
- Marked tenderness of the tonsillar area

Treatment of peritonsillar abscess

- drainage of the abscess and tonsillectomy

Indication for tonsillectomy for tonsillopharyngitis patients

- ✓ quality of life is affected significantly by **recurrent acute pharyngitis secondary to GAS**
  - ➢ 3 episodes yearly for ≥ 3 years or
  - ➢ 5 episodes yearly for 2 years or
  - ➢ 7 episodes in 1 year.
  - ☛ Before considering tonsillectomy, each episode of pharyngitis should be clearly documented with one or more of the following clinical features:
    1. temperature >38.3°C
    2. cervical adenopathy
    3. tonsillar exudate, or
    4. positive test for group A streptococcal (GAS) infection
- ✓ recurrent peritonsillar abscess
- ✓ suspected malignancy
- ✓ obstructive sleep apnea
- ✓ in rare cases, halitosis caused by cryptic tonsils and tonsilloliths (tonsil stones).

Prevention of transmission

- GAS can spread among close contacts, leading to clusters of cases and recurrent infections in households or other close-contact settings.
- The rate of GAS transmission from an infectious case to close contacts is estimated to be between 5 and 50 %.
- Antibiotic use believed to eliminate GAS from the oropharynx in about 80 to 90 % of cases after 24 hours of therapy.
- If untreated, approximately 50% of patients with streptococcal pharyngitis will continue to harbor GAS in the oropharynx 3 to 4 weeks after symptom onset.

Prevention methods

- Hand hygiene
- Postexposure prophylaxis
    - **Testing and treatment of asymptomatic persons** who have been exposed to a patient with GAS pharyngitis are **not routinely recommended**
    - **Indication** for post exposure prophylaxis
        - Patients with a **history of ARF during outbreaks of ARF and/or PSGN**, or
        - When GAS infections are **recurring in households or other close-contact settings.**

3.7.2 Asthma (አስም)

- Asthma is a syndrome characterized by airflow obstruction that leads to excessive narrowing with consequent reduced airflow.
- It is a heterogeneous disease with special type of inflammation in the airways.
- Narrowing of the airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible airflow obstruction.

Epidemiology

- ✓ Asthma is **one of the most common chronic diseases globally** and affects ~300 million people worldwide, with ~250,000 deaths annually.
- ✓ More common in developed countries where it affects,10-12% of adults and 15% of children
- ✓ In developing countries there is a rising prevalence associated with increased urbanization.
- ✓ Occur at any age, peak at 3 years. 50% develop before the age of 10 and another 35% before 40
- ✓ During Childhood M: F = 2:1 and in adulthood the ratio equalize.

RISK FACTORS AND TRIGGERS

- Asthma is a heterogeneous disease with **interplay between genetic and environmental factors.**
- Risk factors distinguished from triggers; **Risk factors** are those which **predispose someone to develop asthma. Triggers** are environmental factors that **worsen asthma in a patient with established asthma.** i.e. trigger airway narrowing, wheezing, and dyspnoea in asthmatic patients.

- **ENDOGENOUS FACTORS**
  - Genetic Predisposition
  - Atopy
    - Atopy is the major risk factor for asthma
    - Patients with asthma commonly suffer from other atopic diseases, particularly allergic rhinitis, which may be found in > 80% of asthmatic patients, and atopic dermatitis (eczema).
    - Atopy is due to the genetically determined production of specific IgE antibody, with many patients showing a family history of allergic diseases.
    - It is likely that environmental factors in early life determine which atopic individuals become asthmatic.
  - Obesity → an independent risk factor for asthma, particularly in women
  - Gender

- **ENVIRONMENTAL FACTORS**
  - Occupational Exposure
    - **Occupational asthma** may be suspected when symptoms improve during weekends and holidays.
    - Occupational asthma is relatively common and may affect up to 10% of young adults
    - Cleaners commonly develop occupational asthma owing to exposure to aerosols of cleaning liquids.
  - **Indoor and outdoor Air Pollution → Indoor air pollution is common risk factor in our set up**
    - Indoor air pollution is also important risk factor with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. maternal smoking is a risk factor for asthma.
  - Diet
    - The role of dietary factors is controversial.
    - Diets low in antioxidants such as vitamin C and vitamin A, magnesium, selenium, and omega-3 PUFA (fish oil) or high in sodium and omega-6 PUFA are associated with an increased risk of asthma.
    - Vitamin D deficiency may also predispose to the development of asthma.
    - Some foods such as **shellfish** and **nuts** may induce anaphylactic reactions that may include wheezing.
  - Acetaminophen → may be linked to **increased oxidative stress** especially in children

N.B Smokers with asthma have more severe disease, more frequent hospital admissions, a faster decline in lung function, and a higher risk of death from asthma than non-smoking asthmatics. Interferes with the anti-inflammatory actions of corticosteroids

- **Triggers**
    - Allergens
        - Allergens Are derived from house dust mites, cat and dog fur, cockroaches (in inner cities), grass and tree pollens, and rodents (in laboratory workers).
        - Other allergens, including grass pollen, ragweed, tree pollen, and fungal spores, are seasonal.
        - Pollens usually cause allergic rhinitis rather than asthma
    - **Infections**
        - URTI such as Rhinovirus, RSV and corona virus are triggering agents
        - Atypical bacteria, such as *Mycoplasma* and *Chlamydophila*, have been implicated in the mechanism of severe asthma.
        - There is an increase in airway inflammation with increased numbers of eosinophils and neutrophils.
    - Drugs → e.g. Beta blockers like Propranolol, Metoprolol
    - Stress
    - Exercise and hyperventilation
        - ***Exercise-induced asthma*** (EIA) typically *begins after exercise has ended*, and *recovers spontaneously within about 30 minutes.*
    - Cold Air
    - Irritants (household sprays, paint fumes)

- Other Factors
    - Lower maternal age
    - Duration of breastfeeding
    - Prematurity and low birth weight
    - Inactivity

Pathophysiology of asthma

- Asthma is associated with a specific chronic inflammation of the respiratory mucosa from the trachea to terminal bronchioles with a predominance in the bronchi (cartilaginous airways)
- Airway inflammation in asthma is associated with airway hyper responsiveness (AHR)
    - **AHR** is the characteristic physiologic abnormality of asthma and *describes the **excessive Broncho constrictor response to multiple inhaled triggers** that would have no effect on normal airways.*
- Mediated by various inflammatory cells and their products
- **Chronic inflammation** is associated with structural changes in the airway called **airway remodeling**
- Limitation of airflow
    - ✓ Bronchoconstriction(mainly)

  - ✓ Airway edema
  - ✓ Vascular congestion
  - ✓ Luminal occlusion with exudate
- ❖ All the above results in
  - ✓ Decrease FEV1, FEV1/FVC ratio & PEF
  - ✓ Increase airway resistance and RV

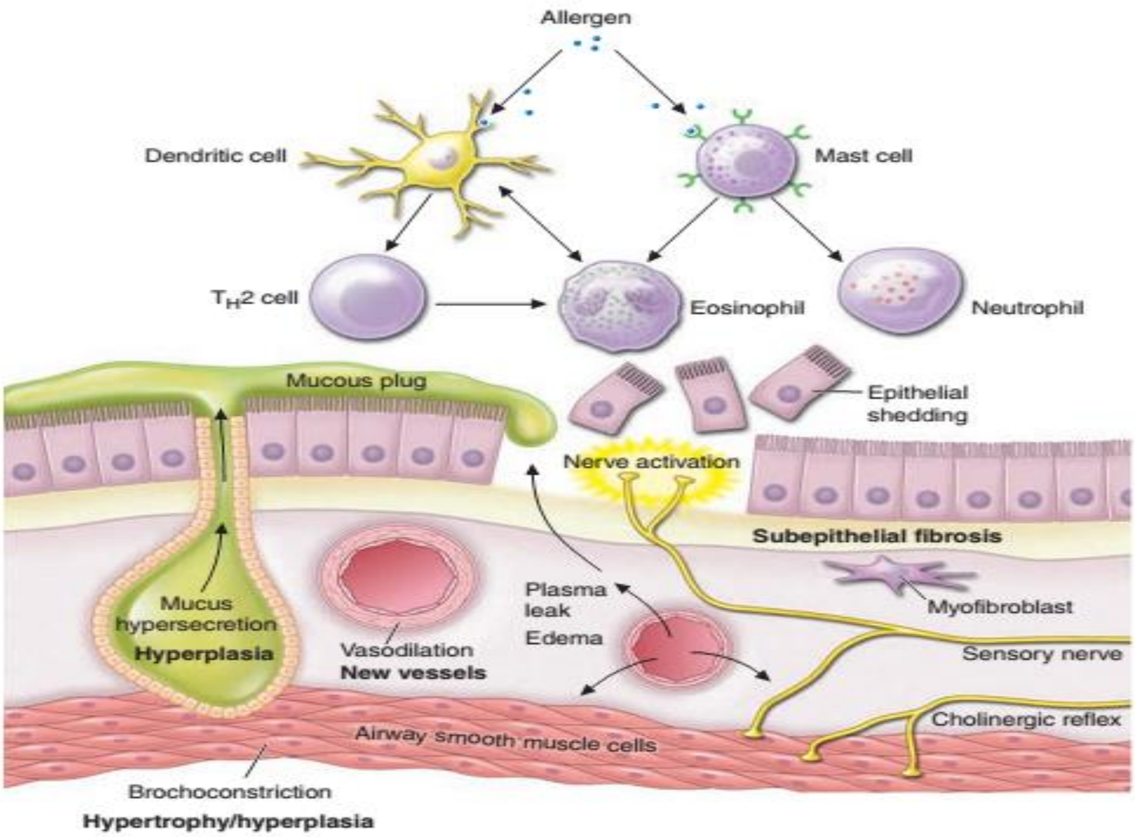

Allergen
Dendritic cell
Mast cell
T_H2 cell
Eosinophil
Neutrophil
Mucous plug
Epithelial shedding
Nerve activation
Subepithelial fibrosis
Mucus hypersecretion
Hyperplasia
Vasodilation
New vessels
Plasma leak
Edema
Myofibroblast
Sensory nerve
Cholinergic reflex
Airway smooth muscle cells
Brochoconstriction
Hypertrophy/hyperplasia

FIGURE 281-3 The pathophysiology of asthma is complex with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

Figure; Pathophysiology of asthma;

- The two net results of pathophysiologic changes are;
  - Airway obstruction (i.e. occlusion of the airway lumen by a mucous plug, which is secreted from hyperplastic goblet cells) and
  - Bronchoconstriction due to different neuro chemokine factors
- Inhaled allergens activate mast cells with bound IgE directly leading to the immediate release of Broncho constrictor mediators, resulting in the early response that is reversed by bronchodilators.
- The most common allergens to trigger asthma are *Dermatophagoides* species.
- The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells.
- The characteristic finding of Airway remodelling is thickening of the basement membrane due to sub epithelial collagen deposition.
  - It is the main cause of chronic asthma, which may later exacerbate due to different triggering agents.
- The epithelium is often shed or friable, with reduced attachments to the airway wall and increased numbers of epithelial cells in the lumen.

- The airway wall itself may be thickened and oedematous (i.e. thickening of basement membrane and smooth muscle).
- And **there is occlusion of the airway lumen by a mucous plug** in fatal asthma. which is comprised of mucous glycoproteins secreted from goblet cells (from goblet cell hyperplasia which leads to mucus hyper secretion) and plasma proteins from leaky bronchial vessels.
- There is also vasodilation and increased numbers of blood vessels (angiogenesis). The airways may be narrowed, erythematous, and oedematous.
- **Mast cells,** which are found at the airway surface in asthma patients and also in the airway smooth-muscle layer, **are important in initiating the acute Broncho constrictor responses** to allergens and several other indirectly acting stimuli, by releasing several Broncho constrictor mediators
- **Multiple inflammatory mediators** (histamine, PG D2, and leukotriene) **contract airway smooth muscle**, increase micro vascular leakage, increase airway mucus secretion, and attract other inflammatory cells. **With final effect of Bronchospasm, Mucus secretion, AHR, & Structural changes.**
- **Cysteinyl-leukotrienes** are **potent Broncho constrictors;**
- Cholinergic pathways, through the release of **acetylcholine acting on muscarinic receptors**, **cause bronchoconstriction** and may be activated reflexly in asthma.

Different phenotypes of asthma.

- Atopic (extrinsic)
- Non-atopic (intrinsic)
- Occupational asthma
- Aspirin-sensitive and
- Paediatric asthma

Clinical features of asthma

- The characteristic symptoms of asthma are wheezing, dyspnea, and coughing, *which are variable, both spontaneously and with therapy*

Symptoms

- **Wheezing (audible wheeze)**
  - The mere presence of wheezing doesn't mean asthma and Lack of wheezes does not exclude asthma.
  - Wheezing in **asthmatic patients** is mostly **diffuse and bilateral**
  - Persistent **wheezing in a specific area** of the chest may indicate endobronchial obstruction with a foreign body **(FBA).**
  - Left ventricular failure (**cardiac asthma)** may mimic the wheezing of asthma but basilar crackles **(basal rales)** are present in contrast to asthma

  - **Upper airway obstruction** by a tumor or laryngeal edema can mimic severe asthma, *but patients typically present with* ***stridor*** *localized to large airways.*
- **Dyspnea**
- **Chest tightness**
- **Cough** → may be associated with Tenacious mucus-difficult to expectorate
- Difficulty in filling their lung with air.
- Nasal itching and sneezing

Physical signs

- Wheeze
- Inspiratory, and to a greater extent expiratory rhonchi
- Hyperinflation
- Respiratory distress
- Skin lesion, Nasal discharge → may be related with atopy

- **Symptoms may be worse at night and patients typically awake in the early morning hours.**
  - Circadian variations in **Broncho motor tone and bronchial reactivity reach their nadir** between 3 AM and 4 AM (i.e. between 9 and 10 NLT), *increasing symptoms of bronchoconstriction.*
- Some patients, particularly children, may present with a predominant non-productive cough **("cough-variant asthma").**
- Prodromal symptoms may precede an attack
  - Itching under the chin
  - Discomfort between the scapulae
  - Inexplicable fear (impending doom).
- Danger signs during acute attacks:
  - Paradoxical breathing
  - Profound diaphoresis
  - Cyanosis
  - Exhaustion Arrhythmia
  - Silent chest on auscultation
  - Mental status change (Drowsiness or confusion)
  - Agitation
  - SPO2 < 90 %

Features suggesting an alternate or comorbid condition

- Fever, Purulent sputum production, Urticaria, or Pleuritic chest pain should raise the possibility of an alternative diagnosis such as pneumonia, flare of bronchiectasis, anaphylaxis, or pneumothorax.

Impending respiratory failure:

- Cyanosis, inability to maintain respiratory effort, depressed mental status, SpO_2 <90%
- $PaCO_2$ >40 mmHg

Diagnosis of asthma

1. Most of the time **asthma is a clinical diagnosis**
2. Spirometry
    - asthma FEV1 ↓sed but FVC is normal so FEV1/FVC ratio decreased.
        - ☛ In restrictive lung disease FEV1 and FVC decreased simultaneously so the FEV1/FVC ratio is normal.
    - Asthma a >12% and 200-ml increase in FEV1 15 min after an inhaled short-acting β2-agonist (SABA; such as inhaled albuterol 400 μg) or in some patients by a 2 - 4-week trial of oral corticosteroids (OCS) (prednisone or prednisolone 30—40 mg daily). But not in COPD.
3. Bronchoprovocation testing
4. Imaging (CXR &HRCT)

3.7.3.1 Acute asthma exacerbations

- Asthma exacerbations are Acute or subacute worsening in symptoms and lung function from the patient’s usual status.
- May occur in patients with a pre-existing diagnosis of asthma or occasionally as the first presentation of asthma
- Usually occur in response to exposure to an external agent and poor adherence with controller medication.
- The best strategy for management of acute exacerbations of asthma is *early recognition* and *intervention*, before attacks become severe and potentially life-threatening.
- **Detecting exacerbations**
    - **Symptoms** → Breathlessness, Wheezing, Cough, and, Chest tightness
    - **Peak flow** → Provides an assessment of the severity of airflow limitation

Table; Severity of Asthma exacerbations

Parameters	Mild	Moderate	Severe
Dyspnea	While talking	At rest	At rest
Talks in	Sentences	Phrases	Words
Comfortable Position	Can lie down	Prefers sitting	Sits up-right
RR	Increased	Increased	Often>30/min
PR	<100	100-120	>120
SpO_2 (on air)	>95%	90-95%	<90%
Use of accessory muscles	Usually not	Commonly	Usually

Wheeze	Often end expiratory	Throughout expiration	Throughout breathing cycle
Pulsus paradoxus (i.e. a fall in SBP by at least 12 mmHg during inspiration which is an indicative of severe airflow obstruction)	Absent	May be present	Often present
Mentation	Alert	Usually agitated	Agitated
A decrement in PEF (peak expiratory flow) from normal, or from the patient's personal best value	> 20 %	20 - 50 %	> 50 % (i.e. PEF < ***50 %*** of baseline)

Acute severe asthma

- Exacerbations of asthma are feared by patients and may be life threatening.

Clinical Features

- Patients are aware of increasing chest tightness, wheezing, and dyspnea that are often not or poorly relieved by their usual reliever inhaler.
- In severe exacerbations patients may be so breathless that they are unable to complete sentences and may become cyanotic.
- Examination usually shows increased ventilation, hyperinflation, and tachycardia.
- Pulsus paradoxus may be present, but this is rarely a useful clinical sign.
- There is a marked fall in spirometric values and PEF.
- Arterial blood gases on air show hypoxemia, and PCO_2 is usually low due to hyperventilation.
- A normal or rising PCO_2 is an indication of impending respiratory failure and requires immediate monitoring and therapy.

Risk factors for fatal asthma

- Previous severe exacerbation (e.g. intubation or ICU admission)
- Hospitalization for asthma in the past year
- Three or more emergency department visits for asthma in the past year
- Not currently using inhaled glucocorticoids
- Recent or current course of oral glucocorticoids
- Use of more than one canister of short-acting beta agonist per month
- Difficulty perceiving asthma symptoms or severity of exacerbations
- History of poor adherence with asthma medications and/or written asthma action plan
- Illicit drug use and major psychosocial problems, including depression
- Comorbidities, such as cardiovascular or chronic lung disease

Asthma medications → can be divided as;

- **Bronchodilators**
- **Controllers**

1) Bronchodilators

- Bronchodilators act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma.
- This gives rapid relief of symptoms but has little or no effect on the underlying inflammatory process.
- Thus, bronchodilators are not sufficient to control asthma in patients with persistent symptoms.
- There are three classes of bronchodilator in current use:
    1. **β2-agonists**
        - Short acting beta$_2$ /β_2/ agonists **(SABA) → e.g. Salbutamol**
            - Have a duration of action of 3 - 6 h, used as needed for immediate symptom relief (relievers).
            - **SABA are the main stay of treatment and most effective bronchodilators during exacerbations**
            - **Salbutamol (Albuterol) Inhaler is available in Ethiopia.**
        - Long acting beta$_2$ agonists **(LABA) → e.g. Salmeterol,** Formoterol
            - **Usually available as Combination of ICS and bronchodilators → e.g. fluticasone/salmeterol,** budesonide/formoterol
            - Have a duration of action of more than 12h and given BID
            - LABAs should not be used as monotherapy since they have no anti-inflammatory effect. Use with inhaled corticosteroids.
            - They should not be used for symptom relief or exacerbations.
    2. **Anti-cholinergic (e.g. ipratropium bromide)** → prevent cholinergic nerve-induced bronchoconstriction and mucus secretion. They are less effective than β2-agonists in asthma therapy as they inhibit only the cholinergic reflex component of bronchoconstriction
    3. **Theophylline (e.g. aminophylline)** → It has now fallen out of favor as **side effects are common, and inhaled β2-agonists are much more effective as bronchodilators**[19]

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[19] The 2021 STG for general hospitals of Ethiopia recommend that, ''Sustained-release theophylline preparations (e.g. **theophedrine 120/11mg** tablets daily to QID base) are effective in controlling nocturnal symptoms and as added therapy in patients with moderate or severe persistent asthma whose symptoms are inadequately controlled by ICS''.

- of these, β2-agonists are by far the most effective

2) Controllers

- Controllers act primarily to inhibit the underlying inflammatory process
- They are taken daily independent of symptoms to achieve and maintain control of persistent asthma.
- Important long-term control medications include
  - Corticosteroids → **ICS** (inhaled corticosteroids) or **OCS** (oral corticosteroids)
  - Anti-leukotrienes → e.g. montelukast, zafirlukast. **montelukast (adult dose 10 mg once daily**
  - Chromones → e.g. cromolyn sodium, nedocromil sodium
  - Steroid sparing → e.g. methotrexate, cyclosporine, azathioprine, gold, IV gamma globulin
  - Anti IgE → omalizumab

Currently, Anti-leukotrienes, Chromones**,** Steroid sparing, and Anti IgE are **not available in most set ups of Ethiopia**

Corticosteroids

- Corticosteroids are the most potent and consistently effective anti-inflammatory agents currently available.
- They decrease both acute and chronic inflammation, resulting in reduced symptoms and improved lung function.
- These agents may also potentiate the action of beta-adrenergic agonists.
- **ICS (inhaled corticosteroids)**
  - **ICS** (See tables below) **are by far the most effective controllers in the management of asthma and are beneficial in treating asthma of any severity and age.**
  - ICS are usually **given BID**, but some may be effective **once daily** in mildly symptomatic patients.
  - ICS rapidly improve the symptoms of asthma, and lung function improves over several days.
  - They are **effective in preventing asthma symptoms**, such as EIA (Exercise induced asthma) and nocturnal exacerbations, but **also prevent severe exacerbations.**
  - ICS reduce AHR (Airway hyperresponsiveness), but maximal improvement may take several months of therapy.

  - Early treatment with ICS appears to prevent irreversible changes in airway function that occur with chronic asthma. **Withdrawal of ICS results in slow deterioration of asthma control**, indicating that they suppress inflammation and symptoms, **but do not cure the underlying condition**.
  - **ICS are now given as first-line therapy for patients with persistent asthma, but if they do not control symptoms at low doses, it is usual to add a LABA as the next step.**
- **Systemic Corticosteroids**
  - Corticosteroids are used **intravenously (hydrocortisone** or methylprednisolone) for the treatment of acute severe asthma
  - A course of **OCS** (usually prednisone or **prednisolone 30 - 45 mg once daily for 5 - 10 days**) is used **to treat acute exacerbations of asthma;** no tapering of the dose is needed.
  - Approximately 1% of asthma patients may require maintenance treatment with OCS; the lowest dose necessary to maintain control needs to be determined.
  - Steroid-sparing therapies may be considered if side effects are a significant problem.

- **Add-on azithromycin (500mg, 3X/week or 250mg daily)** for adult patients with persistent symptomatic asthma despite moderate-high dose ICS and LABA **reduced asthma exacerbations.**

Table: Inhaled corticosteroids (ICS) and Combinations for Adults and adolescents (≥12 years)

Inhaled corticosteroid	Total daily dose (µg)		
	Low	Medium	High
Fluticasone/salmeterol (DPI)	100/50	250/50	500/50
Budesonide/formoterol *(HFA-pMDI)	80/4.5	160/4.5	320/9
Beclomethasone dipropionate **(CFC)**	200 - 500	500 -1000	>1000
Beclomethasone dipropionate (HFA)	100 - 200	200 — 400	>400
Budesonide (DPI)	200 - 400	400 — 800	>800
Fluticasone propionate (DPI or HFA)	100 - 250	250 — 500	>500
Mometasone furoate (HFA-pMDI)	200-400		400

DPI → *Dry Powder inhaler,* **MDI** → *Metered dose inhaler,* **CFC** → *Chloro flouro carbon,* **HFA** → *Hydro flouro alkane*

* When Budesonide/formoterol is prescribed as maintenance and reliever therapy, the maximum recommended dose of formoterol in a single day is 72 µg.

Aims of Asthma Therapy

- Minimal (ideally no) chronic symptoms, including nocturnal
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) use of a required β2-agonist
- No limitations on activities, including exercise
- Peak expiratory flow circadian variation <20%
- (Near) normal PEF (Peak expiratory flow)
- Minimal (or no) adverse effects from drugs

The basic principles of care

- ✓ Assess the ***severity*** of the attack
- ✓ Assess potential ***triggers***
- ✓ Use inhaled ***short-acting beta agonists*** early and frequently, and consider concomitant use of ***ipratropium*** for severe exacerbations
- ✓ Start ***systemic glucocorticoids*** if there is not an immediate and marked response to the inhaled short-acting beta agonists
- ✓ Make frequent (every one to two hours) objective assessments of the ***response*** to therapy until definite, sustained improvement is documented
    - **Good response** → no wheezing or dyspnea (tachypnea in children), PEF > 80 % predicted or personal best
    - **Incomplete response** → persistent wheezing and dyspnea, PEF 50 - 79 % predicted or personal best
    - **Poor response** → Marked wheezing or dyspnea, PEF < 50 % predicted or personal best
    - ☛ *What shall we do for each response? → see the algorism below*
- ✓ ***Admit*** patients who do not respond well after four to six hours to a setting of high surveillance and care
    - *In our set up;* Mild and moderate Acute asthma exacerbations can be managed and discharged from emergency department (usually from triage) after stabilizing the patient (discharge should be after asthma education and appointment is given).
    - Admit patients with **severe attack** persisting after initial treatment in the **emergency room or wards,** and those with **life threatening attacks directly to ICU.**

- ✓ ***Educate*** patients about the principles of ***self-management*** for early recognition and treatment of a recurrent attack and develop an "asthma action plan" for recurrent symptoms → look at below
- ✓ Positioning → sitting upright and/or leaning.
- ✓ Consider IV hydration if necessary

Caution!!! Do not give any form of sedatives during acute attacks

Management of Mild or moderate Acute Asthma exacerbations

- ✓ Oxygen → if there is desaturation or significant dyspnea
  - ▪ Start with 2L/min of Intranasal O_2, increase flow rate accordingly until oxygen saturation of > 90% is achieved
- ✓ Salbutamol (SABA) PLUS
  - ☛ 4 to 6 puffs every 20 minutes in the first 1-4 hours. Then the same dose every 1-4 hours depending on the patient need. OR
    - ○ E.g. Salbutamol puff, 4 puffs every 20 minutes in the first 1 hour, then 4 puffs every 1 hour for 4 hours then, 4 puffs every 4hr for 24 hours.
  - ☛ 2 - 5mg every 20 minutes for 3 doses, then 2.5 - 10mg every 1 - 4 hours as needed, or 10 - 15mg/hour continuously
- ✓ **Hydrocortisone, 200mg, IV stat.** Further IV doses are needed only if oral dosing is not possible (100mg, IV, TID or QID). Followed by
- ✓ **Prednisolone,** 30 - 45 mg, PO, daily for 5 - 10 days (N.B it is available in 5 mg tab form)
  - ▪ Should be started immediately.
  - ▪ **Discontinuation does not need tapering.**

Practical points for approaching a patient with mild or moderate acute asthma exacerbation

- ✓ Asthma patients (with mild or moderate exacerbations) usually stabilized at medical emergency. Admission required for severe attack or those not responding /persisting/ after initial treatment)

- ✓ Put the patient in sitting position
- ✓ Secure IV line
- ✓ Put on Intranasal oxygen for desaturating patients
  - ▪ Start with 2L/min of Intranasal O_2, increase flow rate accordingly until oxygen saturation of > 90% is achieved, if more than 10 L/min required (in that case consider severe attack), use facemask
- ✓ Give Salbutamol puff, 4 to 6 puffs every 20 minutes in the first 1- 4 hours. Then the same dose every 1 - 4 hours depending on the patient need
  - ▪ *Assess the response* to therapy (dyspnea, Pulse oximetry, wheeze) every one to two hours
- ✓ Hydrocortisone, 200mg IV stat.

When patient is stable, discharge with;

- ✓ Salbutamol/SABA/, every 4 to 6 hours as needed
- ✓ Prednisolone, 30 - 45 mg, PO, daily for 5 - 10 days.
- ✓ Appoint after a week (if symptoms improve → discontinue prednisolone, if no improvement, manage as chronic asthma → look at below)
- ✓ Asthma education including how to use MDI → look at below
  - ▪ Even though MDI are used correctly, only 10 - 20 % of Active drug (salbutamol, ICS) is inhaled to lungs. The rest 80 - 90 % is swallowed in to GIT. If there is incorrect use of MDI, obviously the patient will get less than 10 % of the drug to the targeted lung.

Management of acute severe asthma

- One of the main aims of controller therapy is to prevent exacerbations; in this respect, **ICS and combination inhalers** are very effective.
- Systemic corticosteroids
  - ○ Give **IV hydrocortisone 200mg, IV methylprednisolone 40 to 60 mg or oral prednisolone 40 to 60mg**
- A high concentration of **oxygen** should be given by **face mask** to achieve oxygen saturation of > 90% (93 - 95 %).

- **High doses of SABA** → The mainstay of treatment, given either by nebulizer or via an MDI with a spacer.

Interventions to be given based on indication include; → see the algorithm below

- **IV β2-agonists** → may be given for severely ill patients with impending respiratory failure,
- **A nebulized anticholinergic** → may be added if there is not a satisfactory response to β2-agonists alone, as there are additive effects.
    - **Ipratropium bromide** (Anti-cholinergic)
        - 4 - 8 puffs every 20 minutes as needed up to 3 hours. Or
        - 0.25 - 0.5mg every 20 minutes for 3 doses, then as needed.
            - N.B. Ipratropium should be additional therapy to SABA. Can be mixed with SABA during nebulization.
- **A slow infusion of aminophylline** → may be effective in patients who are refractory to inhaled therapies, but it is important to monitor blood levels, especially if patients have already been treated with oral theophylline.
    - **Aminophylline (Theophylline),** 250mg IV bolus slowly over 20 minutes. Maintenance: 0.5mg/kg/hour (maximum: 900mg/day).
        - Decrease the dose to 0.38 mg/kg/hour (maximum: 400mg/day) for
            - Patients with cardiac decompensation
            - Cor pulmonale
            - Hepatic dysfunction
            - Multiorgan dysfunction
            - Old patients (>60 years):

    ☛ **N.B. Aminophylline Should not be first line therapy in the presence of inhaled SABA. Adding it on top of inhaled SABA does not have significant benefit.**

    ☛ Caution!!! When giving Aminophylline to adults who have been on Theophylline tablets, avoid bolus injection as there is a high risk of cardiac arrhythmias, seizures.

- **Magnesium sulfate** → given intravenously or by nebulizer is **effective when added to inhaled β2-agonists**, and is relatively well tolerated **but is not routinely recommended.**
    - **Magnesium sulfate, 2g, IV, infused over 20 minutes, if not previously done**
- **Prophylactic intubation** → may be indicated for impending respiratory failure, when the PCO_2 is normal or rises.
- **Mechanical ventilation** → For patients with respiratory failure, it is necessary to intubate and institute ventilation.
- **General anesthesia** → These patients may benefit from a general anesthetic, such as halothane, if they have not responded to conventional bronchodilators.
- **Antibiotics** → should not be used routinely unless there are signs of pneumonia.

- **Caution!!! Sedatives should never be given as they may depress ventilation.**

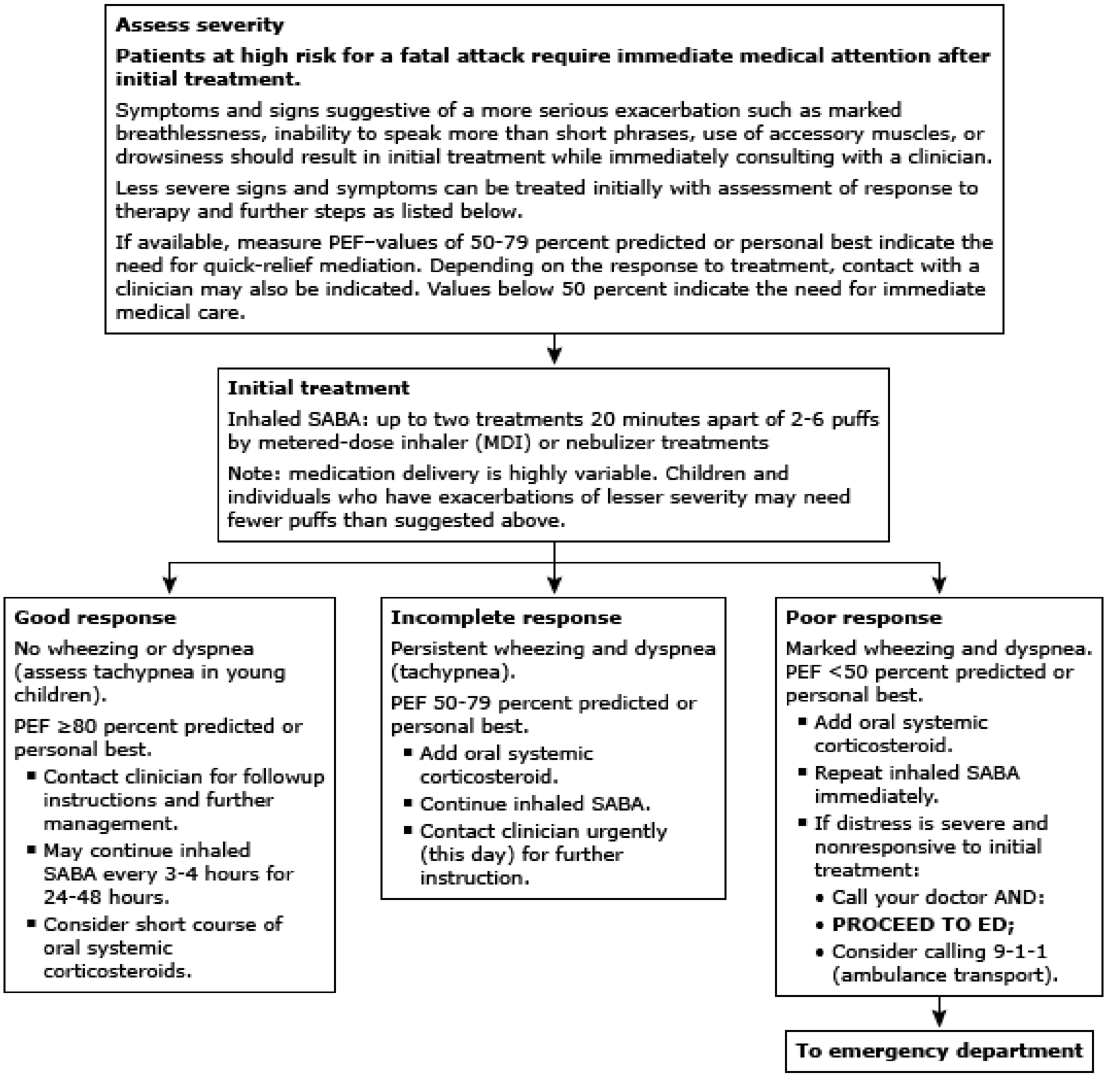
Asthma Education before discharging the patient

- Reduce indoor air pollution by cooking outside or using smokeless cooking stoves
- Avoid allergens that the patient is sensitive to:
  - contact with furry animals (e.g. cats, dogs)
  - Reduce pollen exposure
  - Reduce exposure to house dust mite
- Avoidance of tobacco smoke exposure
  - Provide advice and resources at every visit; advise against exposure of children to ETS (house, car).
- Occupational asthma
  - Ask patients with adult-onset asthma about work history. Remove sensitizers and irritants like dust and fumes as soon as possible. Refer for expert advice, if available.
- Encourage Physical activity
  - Encouraged because of its general health benefits. Provide advice about managing exercise-induced bronchoconstriction.
- Avoid medications that may worsen asthma
  - Always ask about asthma before prescribing NSAIDs or beta-blockers.
- Remediation of dampness or mold in homes
  - Reduces asthma symptoms and medication use in adults.

Goals of asthma education include:

- An explanation of the nature of asthma and its inflammatory basis
- A description of the different classes of drugs and their purpose in treatment (i.e. as-needed “relievers” and regular “controllers”)
- Advice on prevention strategies (allergen, irritant, and tobacco smoke avoidance)
- All patients should be taught how to use their inhalers correctly i.e. the correct choice and use of inhalers and the opportunity to practice under supervision.
- In particular, they need to understand How to recognize worsening asthma and how and when to implement their action plan
- In some patients, particularly those requiring stabilization or patients who have had a recent exacerbation or deterioration, the use of a PEF meter and chart.

Management of asthma exacerbations: home treatment



Assess severity

Patients at high risk for a fatal attack require immediate medical attention after initial treatment.

Symptoms and signs suggestive of a more serious exacerbation such as marked breathlessness, inability to speak more than short phrases, use of accessory muscles, or drowsiness should result in initial treatment while immediately consulting with a clinician.

Less severe signs and symptoms can be treated initially with assessment of response to therapy and further steps as listed below.

If available, measure PEF–values of 50-79 percent predicted or personal best indicate the need for quick-relief mediation. Depending on the response to treatment, contact with a clinician may also be indicated. Values below 50 percent indicate the need for immediate medical care.

Initial treatment

Inhaled SABA: up to two treatments 20 minutes apart of 2-6 puffs by metered-dose inhaler (MDI) or nebulizer treatments

Note: medication delivery is highly variable. Children and individuals who have exacerbations of lesser severity may need fewer puffs than suggested above.

Good response

No wheezing or dyspnea (assess tachypnea in young children).

PEF ≥80 percent predicted or personal best.

- Contact clinician for followup instructions and further management.
- May continue inhaled SABA every 3-4 hours for 24-48 hours.
- Consider short course of oral systemic corticosteroids.

Incomplete response

Persistent wheezing and dyspnea (tachypnea).

PEF 50-79 percent predicted or personal best.

- Add oral systemic corticosteroid.
- Continue inhaled SABA.
- Contact clinician urgently (this day) for further instruction.

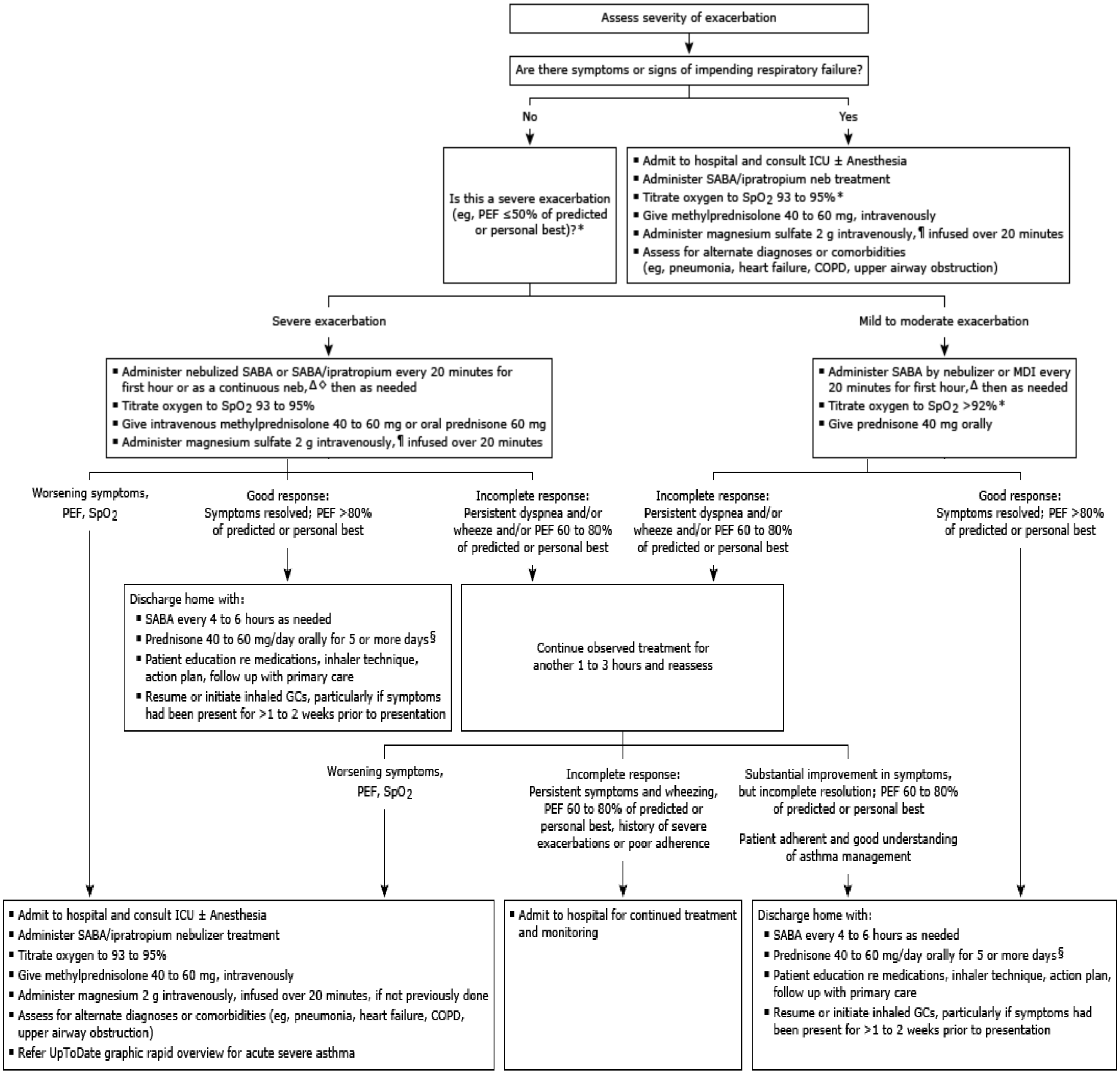
Poor response

Marked wheezing and dyspnea.
PEF <50 percent predicted or personal best.

- Add oral systemic corticosteroid.
- Repeat inhaled SABA immediately.
- If distress is severe and nonresponsive to initial treatment:
  - Call your doctor AND:
  - **PROCEED TO ED;**
  - Consider calling 9-1-1 (ambulance transport).

To emergency department

Management of asthma exacerbations in adults: Emergency department or urgent care



Assess severity of exacerbation

Are there symptoms or signs of impending respiratory failure?

Yes:
- Admit to hospital and consult ICU ± Anesthesia
- Administer SABA/ipratropium neb treatment
- Titrate oxygen to SpO_2 93 to 95%*
- Give methylprednisolone 40 to 60 mg, intravenously
- Administer magnesium sulfate 2 g intravenously,¶ infused over 20 minutes
- Assess for alternate diagnoses or comorbidities (eg, pneumonia, heart failure, COPD, upper airway obstruction)

No: Is this a severe exacerbation (eg, PEF ≤50% of predicted or personal best)?*

Severe exacerbation:
- Administer nebulized SABA or SABA/ipratropium every 20 minutes for first hour or as a continuous neb,Δ◊ then as needed
- Titrate oxygen to SpO_2 93 to 95%
- Give intravenous methylprednisolone 40 to 60 mg or oral prednisone 60 mg
- Administer magnesium sulfate 2 g intravenously,¶ infused over 20 minutes

Mild to moderate exacerbation:
- Administer SABA by nebulizer or MDI every 20 minutes for first hour,Δ then as needed
- Titrate oxygen to SpO_2 >92%*
- Give prednisone 40 mg orally

Worsening symptoms, PEF, SpO_2

Good response: Symptoms resolved; PEF >80% of predicted or personal best

Discharge home with:
- SABA every 4 to 6 hours as needed
- Prednisone 40 to 60 mg/day orally for 5 or more days§
- Patient education re medications, inhaler technique, action plan, follow up with primary care
- Resume or initiate inhaled GCs, particularly if symptoms had been present for >1 to 2 weeks prior to presentation

Incomplete response: Persistent dyspnea and/or wheeze and/or PEF 60 to 80% of predicted or personal best

Incomplete response: Persistent dyspnea and/or wheeze and/or PEF 60 to 80% of predicted or personal best

Continue observed treatment for another 1 to 3 hours and reassess

Good response: Symptoms resolved; PEF >80% of predicted or personal best

Worsening symptoms, PEF, SpO_2

Incomplete response: Persistent symptoms and wheezing, PEF 60 to 80% of predicted or personal best, history of severe exacerbations or poor adherence

Substantial improvement in symptoms, but incomplete resolution; PEF 60 to 80% of predicted or personal best

Patient adherent and good understanding of asthma management

- Admit to hospital and consult ICU ± Anesthesia
- Administer SABA/ipratropium nebulizer treatment
- Titrate oxygen to 93 to 95%
- Give methylprednisolone 40 to 60 mg, intravenously
- Administer magnesium 2 g intravenously, infused over 20 minutes, if not previously done
- Assess for alternate diagnoses or comorbidities (eg, pneumonia, heart failure, COPD, upper airway obstruction)
- Refer UpToDate graphic rapid overview for acute severe asthma

- Admit to hospital for continued treatment and monitoring

Discharge home with:
- SABA every 4 to 6 hours as needed
- Prednisone 40 to 60 mg/day orally for 5 or more days§
- Patient education re medications, inhaler technique, action plan, follow up with primary care
- Resume or initiate inhaled GCs, particularly if symptoms had been present for >1 to 2 weeks prior to presentation

PEF: peak expiratory flow; ICU: intensive care unit; SABA: short-acting beta agonist (eg, albuterol); SpO_2: pulse oxygen saturation; COPD: chronic obstructive pulmonary disease; MDI: metered dose inhaler; GC: glucocorticoid; $PaCO_2$: carbon dioxide tension.

* Titrate oxygen to SpO_2 93 to 95% for patients with severe exacerbations, particularly if at risk for hypercapnia. Aim for SpO_2 >95% in pregnant patients. Titrate to SpO_2 88 to 92%, if asthma-COPD overlap.

¶ Magnesium sulfate is 4.06 mmol/g (2 g = 8.1 mmol).

Δ Please refer to the UpToDate topic on treatment of asthma exacerbations in adults.

◊ Adding ipratropium to albuterol nebulizer treatments is preferred for patients with severe exacerbations; alternatively, SABA/ipratropium can be given via MDI 4 to 8 inhalations every 20 minutes, as needed for up to 3 hours.

§ The dose and duration of therapy can be modified based on the patient's past history of response, severity of exacerbation, and response to current treatment.

3.7.3.2 How to use inhalers for asthma management

- An inhaler is a medical device used for delivering medication into the body via the lungs.
- It is mainly used in the treatment of asthma and COPD.
- The two most common forms are:

    1. Metered-dose inhaler (MDI)
    2. Dry powder inhalers /DPI/ (Accuhalers and turbuhalers)

- Some of the types of inhalers include: Autohalers (Breath Activated aerosol devices), Nebulizers mists and nasal inhalers
- Most patients (up to 80%) cannot use their inhaler correctly. This contributes to poor symptom control and exacerbations.
- To ensure effective inhaler use:
    - ✓ Choose the most appropriate device for the patient before prescribing
    - ✓ check in haler technique at every opportunity
    - ✓ correct using physical demonstrations, paying attention to incorrect steps and confirm that you have checklists.

Metered-dose inhaler (MDIs)

- The medicine is in a small canister, inside a plastic case. When the inhaler is pressed, a measured dose of medicine comes through the mouthpiece.
- MDIs require good technique and coordination by pressing down on the inhaler and breathing in at the same time.
- Because using the inhaler correctly can be difficult, spacer devices are recommended for use with MDIs. The spacer is attached to the MDI to make it easier to use the inhaler and get more medicine into the lungs.

How to use Metered Dose Inhaler

1. Remove the cap and check the mouthpiece is clean and free of objects.
2. Shake the inhaler 4 or 5 times.
3. Holding the inhaler upright with your thumb on the base, breathe out as far as comfortable
4. Place the mouthpiece in your mouth; closing your lips around it to form a good seal - do not bite.
5. Start to breathe in **slowly**; press down firmly on the top of the canister to release a dose; while continuing to breathe in **slowly** and **deeply.**

Figure: Metered Dose Inhaler

6. Removing the inhaler from your mouth; hold your breath for about 10 seconds, or as long as is comfortable.
7. Breathe out gently away from your inhaler mouthpiece
8. For a second dose, wait approximately 30 seconds before repeating steps 2-7
9. Replace the cap

How to use MDI - Click on the link below and watch the video

https://youtu.be/tp479j15x6Q

N.B

Even though MDI are used correctly, only 10 - 20 % of Active drug (salbutamol, ICS) is inhaled to lungs. The rest 80 - 90 % is swallowed in to GIT. If there is incorrect use of MDI, obviously the patient will get less than 10 % of the drug to the targeted lung. → look at the image

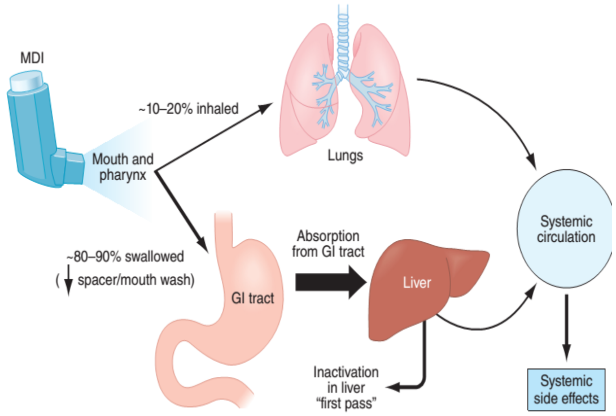

MDI
~10–20% inhaled
Mouth and pharynx
Lungs
~80–90% swallowed
(↓ spacer/mouth wash)
GI tract
Absorption from GI tract
Liver
Inactivation in liver "first pass"
Systemic circulation
Systemic side effects

FIGURE 281-7 Pharmacokinetics of inhaled corticosteroids.

Dry Powder Inhaler (DPI)

- Dry powder inhalers are handheld devices that deliver medication to the lungs and airways as you inhale through it.
- Examples of dry powder inhalers include: **Turbuhaler; Accuhaler; Handihaler; Ellipta inhaler and Breezhaler.**
- The common forms **available in Ethiopia** are **Turbuhaler (eg.Symbicort) and Accuhaler (eg. Seritide)**

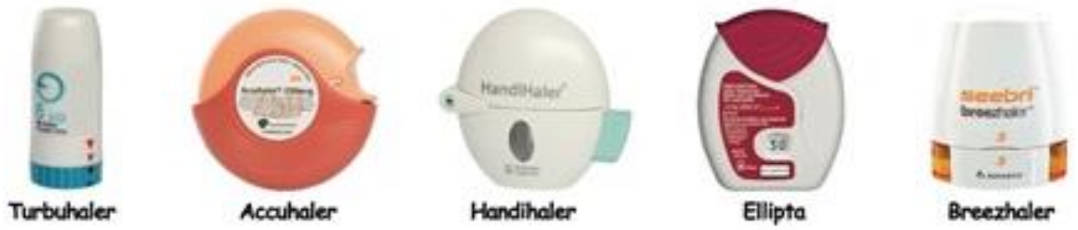


Figure: Different forms of devices delivering DPIs

How to use Accuhaler® (Dry powder inhaler-DPI)

1) Check dose counter.
2) Open cover. (Use thumb grip)
3) Hold the casing of the Accuhaler® in one hand while sliding the thumb grip away until a click is heard
4) Holding your Accuhaler® with the mouthpiece towards you slide the lever away from you until a click is heard. This makes the dose available for inhalation and moves the dose counter on.

Figure: Dry Powder Inhaler (Accuhaler)

5) Holding the inhaler horizontally, breathe out as far as comfortable

6) Place the mouthpiece in your mouth; closing your lips around it to form a good seal - do not bite
7) Breathe in as strongly and deeply as possible
8) Removing the inhaler from your mouth; hold your breath for about 10 seconds, or as long as is comfortable
9) Breathe out gently away from your inhaler mouthpiece
10) To close the Accuhaler®, slide the thumb grip back towards you as far as it will go until it clicks.

How to use Accuhaler® - Click on the link below and watch the video

https://youtu.be/6WOEhIIIHGI

Turbuhaler (DPI)

- Since the turbuhaler is a breath-activated device, to use the turbuhaler properly, you must be able to breathe in deeply. Adults and children 7 years of age and older should be able to use the turbuhaler.

PRESCRIPTION MEDICINE
SYMBICORT
100/6
TURBUHALER
Powder Inhaler
120 doses

Figure: Dry Powder Inhaler (Turbuhaler)

How to use Turbuhaler (DPIs)

1) **Open:** unscrew and remove the cap. Hold the turbuhaler upright.
2) **Load the dose:** twist the base anticlockwise and then back in the other direction until you hear a click. Your turbuhaler is now loaded with one dose of medicine

3) **Breathe out:** breathe out, away from the turbuhaler. Do not blow directly into the turbuhaler.
4) **Inhale your dose:** place the mouth piece in your mouth and form a seal with your lips. Breathe in deeply. Remove the turbuhaler and hold your breath for up to 10 seconds.
5) **Close:** replace the cap and twist until it is on properly.
6) **Cleaning and storing your turbuhaler**: wipe the mouthpiece with a clean dry tissue. Do not wash the mouthpiece or allow it to get wet when cleaning. Keep the cap on when not in use. The device may clog if exhaled or dribbled into or if stored in an area of high humidity with the cap off or unsealed.

How to use Terbuhaler® - Click on the link below and watch the video

https://youtu.be/DqoEdW6dHaI

Common problems when using a turbuhaler

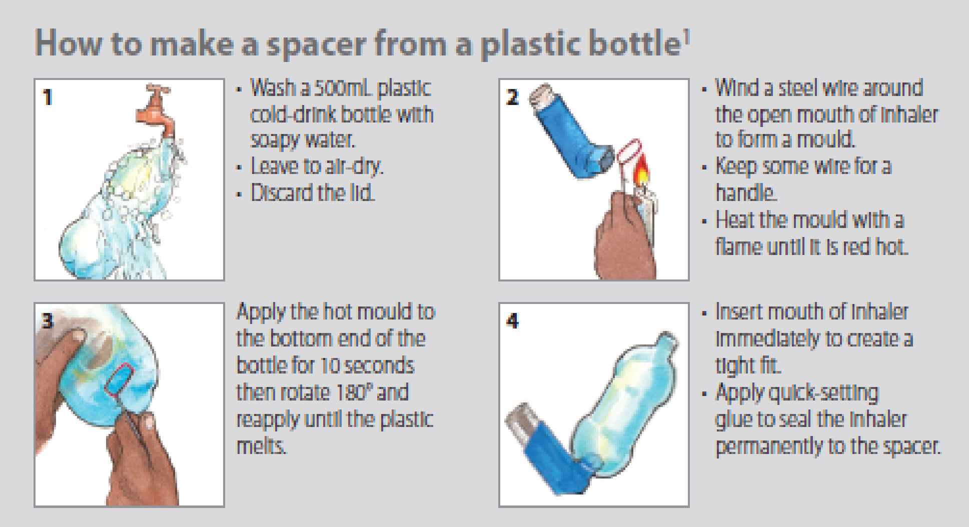
To get the most benefit, it is important to use the correct technique. Here are a few common problems:

- ✓ Not holding your turbuhaler upright (vertical) while loading the dose.
- ✓ Covering the air inlets with your lips.
- ✓ Breathing in through your nose instead of your mouth.
- ✓ Shaking the inhaler to see how much is left.
- ✓ Storing your turbuhaler in a damp place with the cap off.

How to use Spacers

- If patient unable to use an inhaler correctly, add a spacer to increase drug delivery to the lungs, especially if using inhaled corticosteroids. This may also reduce the risk of oral candida.
- Clean the spacer before first use and every second week: remove the canister and wash spacer with soapy water. Allow it to drip dry. Avoid rinsing with water after each use.
- Spacers are not commonly available in Ethiopia so a plastic water bottle. See figure below.

To modify a 500ml plastic bottle for use as an effective spacer



How to make a spacer from a plastic bottle[1]

1
- Wash a 500mL plastic cold-drink bottle with soapy water.
- Leave to air-dry.
- Discard the lid.

2
- Wind a steel wire around the open mouth of inhaler to form a mould.
- Keep some wire for a handle.
- Heat the mould with a flame until it is red hot.

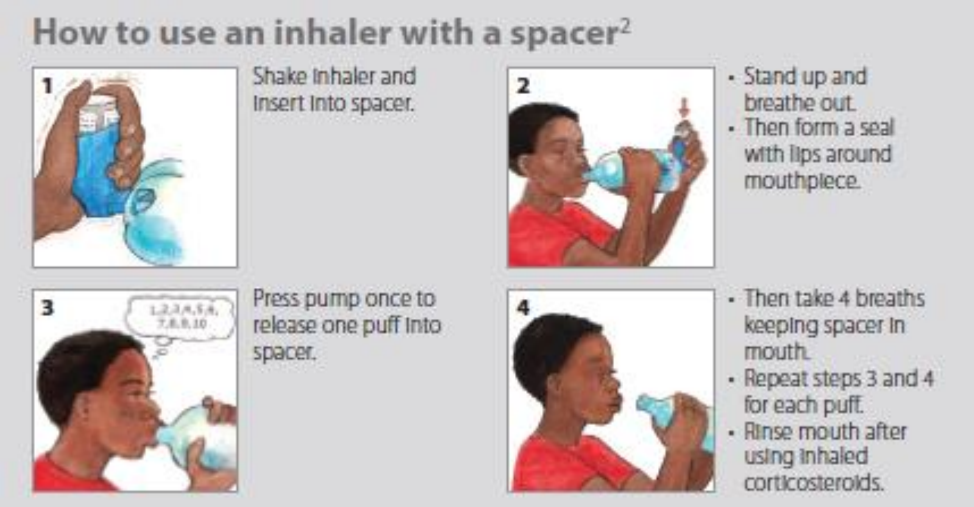
3
Apply the hot mould to the bottom end of the bottle for 10 seconds then rotate 180° and reapply until the plastic melts.

4
- Insert mouth of inhaler immediately to create a tight fit.
- Apply quick-setting glue to seal the inhaler permanently to the spacer.

Figure: How to make a spacer from a plastic bottle

How to use a bottle spacer

Use a modified 500ml plastic bottle in a similar way to a conventional spacer



How to use an inhaler with a spacer[2]

1
Shake inhaler and insert into spacer.

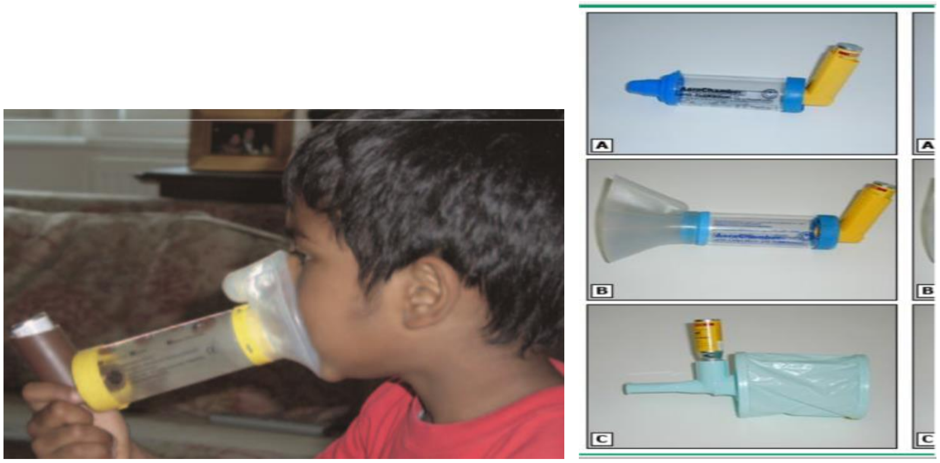
2
- Stand up and breathe out.
- Then form a seal with lips around mouthpiece.

3

Press pump once to release one puff into spacer.

4
- Then take 4 breaths keeping spacer in mouth.
- Repeat steps 3 and 4 for each puff.
- Rinse mouth after using inhaled corticosteroids.

Figure: How to use an inhaler with a spacer



Images; MDI with spacers

How to use an Inhaler with a spacer - Click on the link below and watch the video

https://youtu.be/ma_cmlU9DxU

3.7.3.3 Chronic asthma

- It is a chronic inflammatory disorder of the lower airways in susceptible individuals resulting in recurrent episodes of wheezing, dyspnea on exertion, chest tightness and coughing particularly at night and in early morning on daily basis with undercurrent acute exacerbation and recurrent chest infection
- This inflammation is usually associated with widespread but variable **airflow obstruction that is often reversible** spontaneously or with treatment but in some patients with chronic asthma **there may be an element of irreversible airflow obstruction**
- **Chronic asthmatic response:**
  - Chronic inflammation of mucosa of lower airway → Destruction of airway epithelium by toxic granule contents → epithelial shedding into bronchial lumen → exposure of sensory nerve endings and imbalance in cholinergic and peptinergic neuronal control → **Airway remodeling with subendothelial fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy, vascular changes** → fixed airway obstruction.
- It is important to establish the diagnosis objectively using spirometry or PEF/peak expiratory flow/ measurements at home.
- But **in our setup**, diagnosis using spirometry or PEF may be impossible, so it is better **to differentiate Various severities of asthma using clinical parameters** (see the table below). **These include**
  - **Frequency of symptoms in general**
  - **Frequency of night time symptoms which awaken the patient from sleep**
  - Frequency of using SABA (salbutamol) for symptom control
  - **Interference with normal activity**
  - **Exacerbations requiring OCS**
  - If available, pulmonary function test (FV1, FV1/FVC ratio, PEF)

Table; Classification of severity of asthma

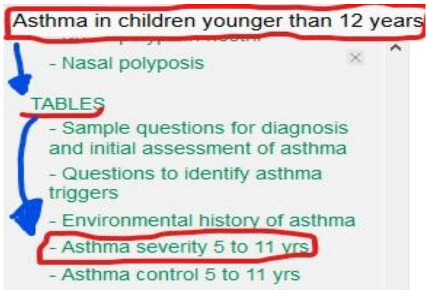
Classifying asthma severity and initiating treatment in youths greater than or equal to 12 years of age and adults

Components of severity		Classification of asthma severity (≥12 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8 to 19 years 85 percent 20 to 39 years 80 percent 40 to 59 years 75 percent 60 to 80 years 70 percent	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3 to 4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80 percent predicted • FEV_1/FVC normal	• FEV_1 ≥80 percent predicted • FEV_1/FVC normal	• FEV_1 >60 but <80 percent predicted • FEV_1/FVC reduced 5 percent	• FEV_1 <60 percent predicted • FEV_1/FVC reduced >5 percent
Risk	**Exacerbations requiring oral systemic glucocorticoids**	**0 to 1/year (see footnote)**	**≥2/year (see footnote)**		
		Consider severity and interval since last exacerbation			
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended step for initiating treatment		Step 1	Step 2	Step 3	Step 4 or 5
				And consider short course of oral systemic glucocorticoids	
		In two to six weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Table; **Assessing severity and initiating treatment for patients who are not currently taking long-term control medications.** The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs. Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs. At present, data are inadequate to correlate frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. **For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic glucocorticoids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.**

FEV_1: forced expiratory volume in one second; **FVC**: forced vital capacity;

Even though this table is for ≥ 12 years of age, it is almost similar for < 12 years age (if you want to cross check the details, look at the table from UpToDate 2018 ''asthma in children younger than 12 years'' as shown in the picture)



Asthma in children younger than 12 years

- Nasal polyposis

TABLES

- Sample questions for diagnosis and initial assessment of asthma
- Questions to identify asthma triggers
- Environmental history of asthma
- Asthma severity 5 to 11 yrs
- Asthma control 5 to 11 yrs

Management of chronic asthma

- Triggers that worsen asthma control, such as allergens or occupational agents, should be avoided, whereas triggers, such as exercise and fog, which result in transient symptoms, provide an indication that more controller therapy is needed.
- It is important to **assess asthma control**, assessed by symptoms, night awakening, need for reliever inhalers, limitation of activity and lung function (see the Table 281 - 4 below)

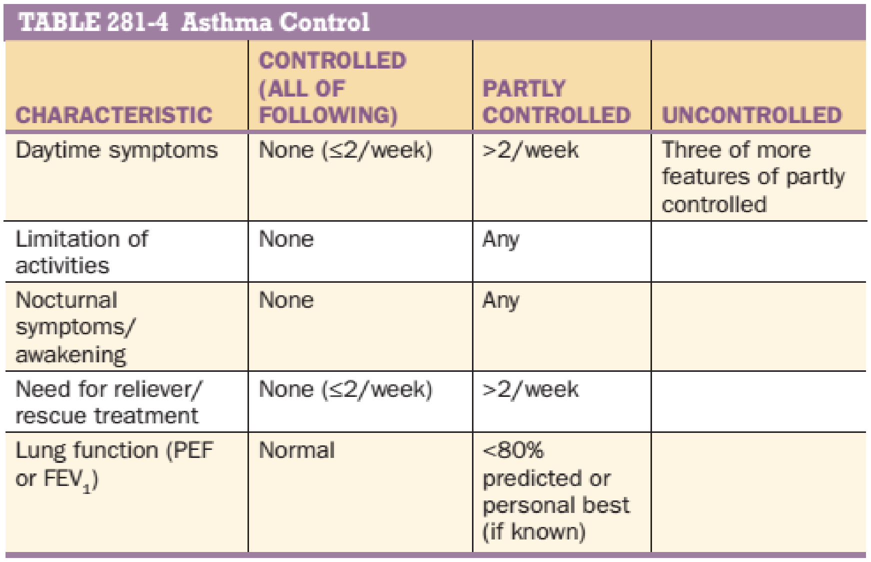


TABLE 281-4 Asthma Control

CHARACTERISTIC	CONTROLLED (ALL OF FOLLOWING)	PARTLY CONTROLLED	UNCONTROLLED
Daytime symptoms	None (≤2/week)	>2/week	Three of more features of partly controlled
Limitation of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (≤2/week)	>2/week	
Lung function (PEF or FEV_1)	Normal	<80% predicted or personal best (if known)	

Patients with poor asthma control should be assessed for the following.

- Reasons for poor adherence and misunderstanding the difference between relievers and controllers
- Poor inhaler technique
- Exposure to trigger factors at home and work
- Presence of gastro-esophageal acid reflux disease (GERD)
- Rhinitis and sinusitis
- Use of medications that may aggravate asthma such as aspirin, NSAID's and β blockers
- Other medical conditions mimicking asthma symptoms (e.g. cardiac disease).

Stepwise therapy of chronic Asthma

- Pharmacologic therapy Depends on the severity of asthma
- Assess the severity of asthma and scale up or down treatment based on the severity.
  - For example, if symptoms are controlled after 3 months decrease the dose

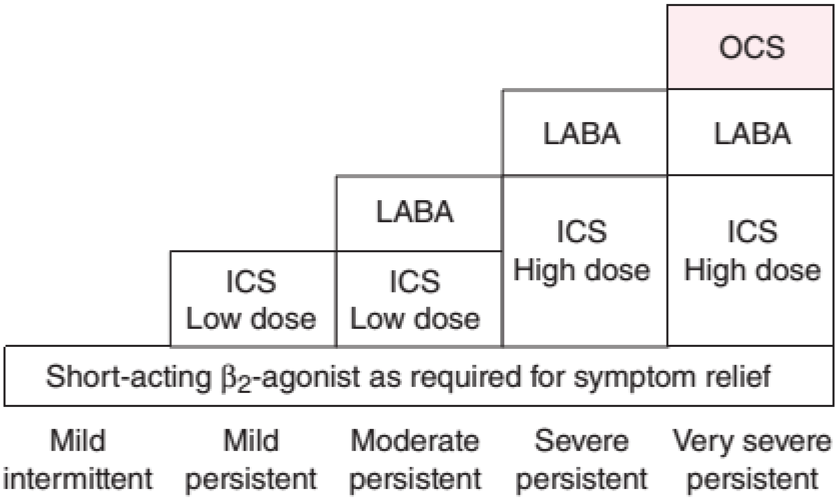

OCS
LABA
LABA
LABA
ICS Low dose
ICS Low dose
ICS High dose
ICS High dose
Short-acting β_2-agonist as required for symptom relief
Mild intermittent
Mild persistent
Moderate persistent
Severe persistent
Very severe persistent

FIGURE 281-8 Stepwise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; OCS, oral corticosteroid.

- For patients with mild, intermittent asthma, a SABA is all that is required. However, use of a reliever medication more than twice a week indicates the need for regular controller therapy.
- The treatment of choice for all patients is an ICS given twice daily. It is usual to start with an intermediate dose (e.g. 200μg BID of beclomethasone dipropionate) or equivalent and to decrease the dose if symptoms are controlled after 3 months.
- If symptoms are not controlled, a LABA should be added, which is most conveniently given by switching to a combination inhaler.
- The dose of controller should be adjusted accordingly, as judged by the need for a rescue inhaler.
- Low doses of theophylline or an antileukotriene may also be considered as an add-on therapy, but these are less effective than LABA.
- In patients with severe asthma, low-dose oral theophylline is also helpful, and when there is irreversible airway narrowing, the long-acting anticholinergic may be tried.
- If asthma is not controlled despite the maximal recommended dose of inhaled therapy, it is important to check adherence and inhaler technique. In these patients, maintenance treatment with an OCS may be needed and the lowest dose that maintains control should be used.
- Once asthma is controlled, it is important to slowly decrease therapy in order to find the optimal dose to control symptoms.

Dose and frequency of drugs used in stepwise management of asthma

Mild Intermittent asthma

First line

- Salbutamol/SABA/, inhaler 200µg/puff, 2 puffs to be taken as needed but not more than 3-4 times a day, or tablet, 2- 4mg 3-4 times a day
    - No daily medication needed. However, use of a reliever medication *more than three times a week* indicates the need for regular controller therapy.

Alternative

- Ephedrine + Theophylline, 11mg + 120mg P.O., BID OR TID

Mild Persistent asthma

- Salbutamol/SABA/, inhaler, 200 µg/puff 2 puffs to be taken, as needed but not more than 3-4 times/day, or tablet, 2 - 4mg 3-4 times a day PLUS
- Beclomethasone/ICS/, oral inhalation, 50 - 100µg, BID.
    - ☛ If symptoms are controlled after three months, decrease the dose (down grade to intermittent dose) to 100µg, BID

Moderate Persistent asthma

- Salbutamol /SABA/, inhalation 200µg//puff, 1 - 2 puffs as needed PRN not more than 3-4 times a day. PLUS
- Beclomethasone/ICS/, oral inhalation 100 - 250 µg, BID.
    - ☛ Decrease the dose to 100 µg, BID if symptoms are controlled after three months. (Preferred if symptoms are mor severe or if response is not optimal to Beclomethasone)

      PLUS
- Fluticasone/Salmeterol (LABA), 250/50 µg oral inhalation, BID

  PLUS (if required)
- Ephedrine + Theophylline, 11mg + 120mg P.O., BID OR TID

Severe persistent asthma

- Salbutamol/SABA/, inhalation 200/puff 1-2µg/puffs as needed PRN not more than 3-4 times a day. PLUS

- Beclomethasone/ICS/, oral inhalation 300 - 400µg, BID.
    - Decrease the dose to 100µg, BID if symptoms are controlled after three months. (Preferred if symptoms are mor severe or if response is not optimal to Beclomethasone)

PLUS

- Fluticasone/Salmeterol (LABA), 250/50µg oral inhalation, BID

PLUS (If required)

- Ephedrine + Theophylline, 11mg + 120mg P.O., BID OR TID

PLUS (if required)

- Prednisolone (OCS), 5 - 10mg P.O. daily.
    - Doses of 20-40mg daily for seven days may be needed for short-term exacerbations in patients not responding to the above treatment.

REVIEWING RESPONSE AND ADJUSTING TREATMENT

- How often should asthma be reviewed?
    - **1-3 months** after treatment started, then **every 3-12 months**.
    - During **pregnancy**, every **4-6 weeks**.
    - **After** an **exacerbation**, within **1 week**.

- Stepping up asthma treatment;
    - **Consider stepping up if** … uncontrolled symptoms, exacerbations or risks
    - First **check for common causes** (symptoms not due to asthma, incorrect inhaler technique, poor adherence, persistent environmental exposures and drugs, comorbidities that may contribute to respiratory symptoms).

    - ***Sustained step-up*, for at least 2-3 months** if asthma poorly controlled;
    - ***Short-term step-up*, for 1-2 weeks**, e.g. with viral infection or allergen;
    - May be initiated by patient with written asthma action plan.

    - ***Day-to-day adjustment;***
    - For patients prescribed low-dose ICS/formoterol maintenance and reliever regimen
- Stepping down asthma treatment;
    - **Consider stepping down if** … symptoms **well controlled for 3 months + low risk for exacerbations.**
    - Stopping ICS is not advised in adults with asthma because of risk of exacerbations

  - Find each patient's **minimum effective dose** that controls both symptoms and exacerbations.

INDICATIONS FOR CONSIDERING REFERRAL TO SPECIALITY CENTER

- Difficulty confirming the diagnosis of asthma
- Suspected occupational asthma
- Persistent uncontrolled asthma or frequent exacerbations
- Risk factors for asthma-related death
- Significant side-effects (or risk of side-effects)
- Symptoms suggesting complications or sub-types of asthma
- Asthma with confirmed food allergy.

Special considerations

Refractory Asthma

- Although most patients with asthma are easily controlled with appropriate medication, a small proportion of patients (~5%) are difficult to control despite maximal inhaled therapy.
- There are two major patterns of difficult asthma:
  - Some patients have **persistent symptoms and poor lung function**, despite appropriate therapy,
  - Whereas others may have **normal or near normal lung function but intermittent, severe (sometimes life-threatening) exacerbations.**
- **The most common reason for poor control of asthma is poor adherence** with medication, particularly ICS. Compliance with ICS may be low because patients do not feel any immediate clinical benefit or may be concerned about side effects.
- There are several factors that may make asthma more difficult to control, including;
  - Exposure to high, ambient levels of allergens or unidentified occupational agents.
  - Severe rhinosinusitis may make asthma more difficult to control
  - Upper airway disease should be vigorously treated.
  - Drugs such as β blockers, aspirin, and other cyclooxygenase (COX) inhibitors like NSAID's may worsen asthma.
  - Some women develop severe premenstrual worsening of asthma, which is unresponsive to corticosteroids and requires treatment with progesterone or gonadotropin-releasing factors.
  - Few systemic diseases make asthma more difficult to control, but hyper- and hypothyroidism may increase asthma symptoms and should be investigated if suspected.

- Bronchial biopsy studies in refractory asthma may show the typical eosinophilic pattern of inflammation, whereas others have a predominantly neutrophilic pattern.
- Structural changes in the airway, including fibrosis, angiogenesis, and airway smooth muscle thickening, are more commonly seen in these patients

Treatment of Refractory Asthma

- Refractory asthma is difficult to control, by definition.
- **Check adherence and the correct use of inhalers technique**
    - **Compliance may be improved by giving the ICS as a combination with a LABA that gives symptom relief.**
- **Identify and eliminate any underlying triggers.**
- **Low doses of theophylline may be helpful** in some patients, and theophylline withdrawal has been found to worsen in many patients.
- Many of these patients will require **maintenance treatment with OCS**, and the minimal dose that achieves satisfactory control should be determined by careful dose titration.
- A few patients may benefit from **infusions of β2-agonists.**
- In some patients with **allergic asthma**, **omalizumab** is effective, particularly when there are frequent exacerbations.

Corticosteroid-Resistant Asthma

- It is defined by a failure to respond to a high dose of oral prednisone/prednisolone (40 mg once daily over 2 weeks), ideally with a 2-week run-in with matched placebo.
- More common is reduced responsiveness to corticosteroids where control of asthma requires OCS (corticosteroid-dependent asthma).
- A few patients with asthma show a poor response to corticosteroid therapy
- Complete resistance to corticosteroids is extremely uncommon
- There are likely to be heterogeneous mechanisms for corticosteroid resistance;

Brittle Asthma

- Some patients show **chaotic variations in lung function despite taking appropriate therapy.**
- **There are two types of brittle asthma**
    - **Type I brittle asthma** → patients with this type, show a persistent pattern of variability and may require OCS or, at times, continuous infusion of β2-agonists

- **Type II brittle asthma** →patients with this type, have generally normal or near-normal lung function but precipitous, unpredictable falls in lung function that may result in death.
  - Difficult to manage as they do not respond well to corticosteroids, and the worsening of asthma does not reverse well with inhaled bronchodilators.
- In some of these patients, there may be allergy to specific foods.
- **The most effective therapy is subcutaneous epinephrine**, which suggests that the worsening is likely to be a localized airway anaphylactic reaction with edema.
- These patients should be taught to self-administer epinephrine and should carry a medical warning accordingly.

Asthma in Pregnancy

- Approximately **1/3rd** of asthmatic patients who are pregnant **improve** during the course of a pregnancy, **1/3rd deteriorate**, and **1/3rd are unchanged**.
- It is important to maintain good control of asthma as poor control may have adverse effects on fetal development (chronic maternal hypoxia is risk factor for both maternal and neonatal complications, e.g. Perinatal asphyxia).
- Adherence may be a problem as there is often concern about the effects of antiasthma medications on fetal development.
- **The drugs have been shown to be safe** and without teratogenic potential.
  - **These drugs include SABA, ICS, and theophylline**;
- There is **less safety information about** newer classes of drugs such as **LABA, antileukotrienes, and anti-IgE.**
- If an OCS is needed, it is **better to use prednisone rather than prednisolone** as it cannot be converted to the active prednisolone by the fetal liver, thus protecting the fetus from systemic effects of the corticosteroid. **There is no contraindication to breast-feeding** when patients are using these drugs.
  - *This note is from Harrison 20th edition. According to UpToDate 2018, Hydrocortisone is Category C, Prednisolone and prednisone are Category C/D*
  - *what do we do for each Category of drugs in pregnancy? Click here* → Chapter 7; Basics about rational use of antibiotics

Asthma in the Elderly

- Asthma may start at any age, including in elderly patients.
- The principles of management are the same as in other asthmatics, but side effects of therapy may be a problem, including muscle tremor with β2-agonists and more systemic side effects with ICS.
- Comorbidities are more frequent in this age group, and interactions with drugs such as β2-blockers, COX inhibitors, and agents that may affect

theophylline metabolism need to be considered. COPD is more likely in elderly patients and may coexist with asthma.

- A trial of OCS may be very useful in documenting the steroid responsiveness of asthma.

ACOS (Asthma COPD Overlap syndrome)

- Refer from COPD under long case of Nitsbin (click here → COPD (Chronic obstructive pulmonary disease))

3.8 GI related disorders and infections

3.8.1 Infectious Diarrheal Disease (የተቅማጥ በሽታ/የተቅማጥ ልክፍት/)

3.8.2 Bloody diarrhoea /ደም የቀላቀለ ሰገራ/

3.8.2.1 Bacillary dysentery /በሲላዊ ተቅማጥ፣ በባክቴሪያ ልክፍት የሚመጣ ተቅማጥ/

- Bacillary dysentery is **diarrheal disease caused commonly by bacteria**, which invade and destroy the intestinal epithelium.

Etiology

- ✓ The 1st three from the following are the dominant bacterial agents causing bloody diarrhea in Ethiopia.

- **Salmonella**
- **Shigella**
- **Campylobacter**
- **E. coli.**
- **Entamoeba histolytica and**
- **S. mansoni**
  - ☛ Transmission occurs via contaminated water or food.

Clinical features

– **watery, mucoid or bloody diarrhea with tenesmus.**

- severe abdominal cramps
- fever

Investigations

- S/E → abundance of leukocytes **(pus cells)**
- Stool culture, if available, can be used to guide treatment selection

Treatment

Supportive treatment

- Correct dehydration with **ORS** (mild to moderate dehydration) or **IV fluids** (severe dehydration) is a cornerstone quality of care indicator for all diarrheal illnesses.
- Diet → continuous provision of nutritious food (small frequent feeding as tolerated)
- Relieve pain and fever if necessary
- The use of anti-motility agents like loperamide is not recommended for dysentery due to the potential for toxic mega colon.

Pharmacologic

Look at table below

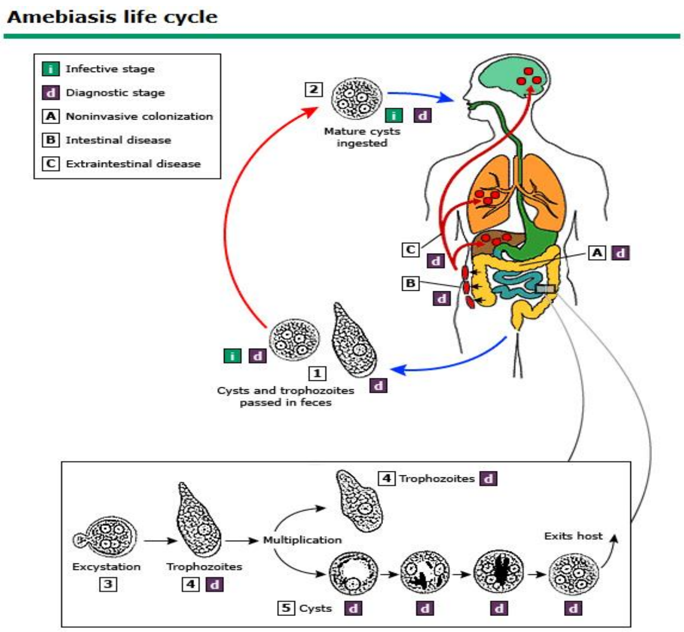
recommendation:

- ☛ A stool examination (including culture studies if available) should be carried before the administration of empiric antibiotics.
- ☛ Fluoroquinolone like ciprofloxacin are empiric first choice agents for 3 to 5 days. If susceptibility data available other drugs (e.g. Cotrimoxazole, macrolides, tetracyclines) can also be used, otherwise better avoided.
- ☛ Sever cases like septicemia should be treated with IV ceftriaxone for at least 7 days.

3.8.2.2 Amoeba (አሜባ)

- Amoebiasis results from infection with the non-invasive Entamoeba dispar or the invasive Entamoeba histolytica
- The 3rd most common cause of death from parasitic disease.

- It is most commonly contracted through ingestion of live cysts found with fecally contaminated water, food, or hands.
- Foodborne infection is caused by fecally contaminated soil or water used for growing vegetables.
- It is endemic in most developing countries including Ethiopia.


Amebiasis life cycle

i Infective stage
d Diagnostic stage
A Noninvasive colonization
B Intestinal disease
C Extraintestinal disease
2
Mature cysts ingested
i d
C d
B d
A d
i d
1
Cysts and trophozoites passed in feces
d
4 Trophozoites d
Multiplication
Exits host
Excystation
3
Trophozoites
4 d
5 Cysts d
d
d
d

Cysts and trophozoites are passed in feces **(1)**. Cysts are typically found in formed stool, whereas trophozoites are typically found in diarrheal stool. Infection by *Entamoeba histolytica* occurs by ingestion of mature cysts **(2)** in fecally contaminated food, water, or hands. Excystation **(3)** occurs in the small intestine and trophozoites **(4)** are released, which migrate to the large intestine. The trophozoites multiply by binary fission and produce cysts **(5)**, and both stages are passed in the feces **(1)**. Because of the protection conferred by their walls, the cysts can survive days to weeks in the external environment and are responsible for transmission. Trophozoites passed in the stool are rapidly destroyed once outside the body, and if ingested would not survive exposure to the gastric environment. In many cases, the trophozoites remain confined to the intestinal lumen (**A:** noninvasive infection) of individuals who are asymptomatic carriers, passing cysts in their stool. In some patients the trophozoites invade the intestinal mucosa (**B:** intestinal disease), or, through the bloodstream, extraintestinal sites such as the liver, brain, and lungs (**C:** extraintestinal disease), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively *E. histolytica* and *E. dispar*. These two species are morphologically indistinguishable unless *E. histolytica* is observed with ingested red blood cells (erythrophagocystosis). Transmission can also occur through exposure to fecal matter during sexual contact (in which case not only cysts, but also trophozoites could prove infective).

Clinical features

- Gradual development of diffuse **lower abdominal or back pain**
- **mild diarrhea**
- Malaise, weight loss
- **If caecum is involved**, signs and symptoms will **mimic** those of **appendicitis** (right lower quadrant pain)
- Full **dysentery** develops in some patients with passage of 10—12 stools per day

- Stools are mostly blood and mucoid

Complications or unusual presentations:

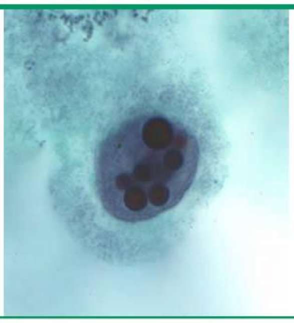
- amoebic liver abscess
- amoebic colitis can be confused with IBD,
- amoeboma (tender abdominal mass)

Investigations

Stool examination:

- ✓ Fresh stools specimens must be examined for trophozoites typical of E. hemolytica. Cysts of both entamoeba species
- ✓ Entamoeba dispar or the invasive Entamoeba histolytica are very similar therefore trophozoites that have ingested red blood cells are diagnostic of E. hemolytica

***Entamoeba histolytica* trophozoite: Microscopy**



Trophozoites of *E. histolytica* with ingested erythrocytes stained with trichrome.

Treatment

Non pharmacologic

- Hydration is important in patients who have severe dysentery

Pharmacologic

Look at table below

3.8.3 Watery diarrhoea /ውሃ የመሰለ ተቅማጥ/

- Watery diarrhea is usually the primary manifestation of an inflammatory or non-inflammatory response to intestinal tract infection.

- **Viral diseases** (Rotavirus, Norovirus, adenovirus…) are the **commonest causes** of watery diarrhea
- **V.cholera** and **E.coli** are common bacterial etiologies.
- Salmonella and listeria may need to be considered in some high-risk patients.
- Bacterial causes usually have high fever or significant abdominal pain, and duration >3 days
- viral causes more likely have non-toxic feature (non bloody, watery stool; mild disease; afebrile)
- For viral causes, no need for investigation and treatment, except supportive measures

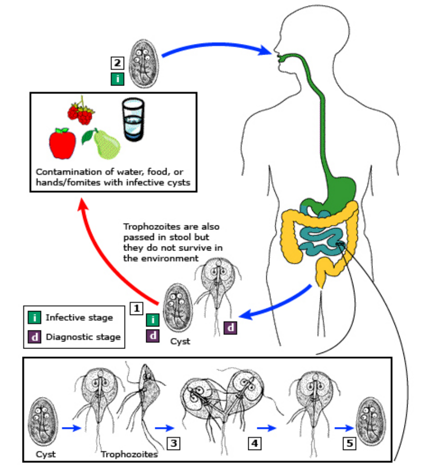
Supportive measures for watery diarrhea

- Fluid and electrolyte replacement is the cornerstone for all diarrhea patients
- Feeding, especially in children
- Antimotility drugs (eg, **loperamide 4mg initially, then 2mg after every loss stool** up to 16 mg/day) will decrease the duration of the illness in immunocompetent adults.
  - Loperamide use should be **avoided** at any age in suspected or proven cases where **toxic megacolon** may result in inflammatory diarrhea or diarrhea with fever.
  - Should be **discontinued after 48 hours if no response**
  - **avoided in paediatrics.**
- Zinc and vitamin A supplementation is associated with a protective effect in children

3.8.3.1 Giardia (ጃርዲያ)

- *Giardia lamblia* is a ubiquitous gastrointestinal protozoon that results in clinical pictures ranging from **asymptomatic (**60%**)** colonization to **acute or chronic diarrheal illness.**
- It can occur both sporadically and in epidemics.
- *Giardia lamblia* infects humans through ingestion of as few as 10 cysts.
- The infection is more prevalent in children than adults.

***Giardia* life cycle**


2
i
Contamination of water, food, or hands/fomites with infective cysts
Trophozoites are also passed in stool but they do not survive in the environment
1
i
d
Cyst
d
i Infective stage
d Diagnostic stage
Cyst
Trophozoites
3
4
5

Cysts are resistant forms and are responsible for transmission of giardiasis. Both cysts and trophozoites can be found in the feces (diagnostic stages) **(1)**. The cysts are hardy and can survive several months in cold water. Infection occurs by the ingestion of cysts in contaminated water, food, or by the fecal-oral route (hands or fomites) **(2)**. In the small intestine, excystation releases trophozoites (each cyst produces two trophozoites) **(3)**. Trophozoites multiply by longitudinal binary fission, remaining in the lumen of the proximal small bowel where they can be free or attached to the mucosa by a ventral sucking disk **(4)**. Encystation occurs as the parasites transit toward the colon. The cyst is the stage found most commonly in nondiarrheal feces **(5)**. Because the cysts are infectious when passed in the stool or shortly afterward, person-to-person transmission is possible. While animals are infected with *Giardia*, their importance as a reservoir is unclear.

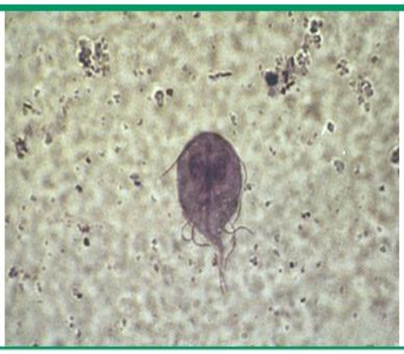
Clinical features

- ☛ The most common presentation is **diarrhea** which is **foul-smelling with fatty stools (steatorrhea)**
- ☛ Flatulence
- ☛ weight loss
- ☛ crampy abdominal pain with bloating
- ☛ failure to thrive.

Investigations

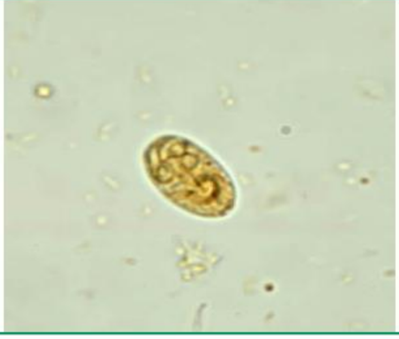
- ✓ *Giardia lamblia* trophozoite or cyst from fecal or duodenal samples.

***Giardia* trophozoite**



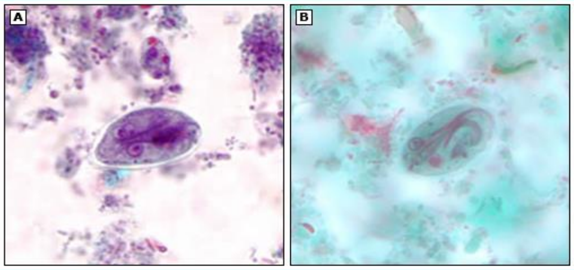
High-power microscopy revealing *Giardia* trophozoite with easily identified flagella. *Giardia* trophozoites measure 10 to 20 micrometers in length.

***Giardia* intestinalis cyst in wet mount stained with iodine**



Giardia cysts measure 8 to 19 mcm (average 10 to 14 mcm).

***Giardia intestinalis* cyst stained with trichrome**



Giardia cysts measure 8 to 19 mcm (average 10 to 14 mcm).

Treatment

Supportive treatment

- ☛ Correction of fluid and electrolyte loses due to the diarrhea

Medicine Treatment

Look at table below

Prevention:

- Avoid drinking water or eating foods likely contaminated (E.g. purify drinking water, do not swallow water while swimming, and eat cooked foods at least in risk conditions).
- Strict hand washing with water and soap, alcohol-based hand rubs are effective for trophozoites but poor for cysts
- Carful diaper disposal and treatment of symptomatic children will prevent spread.
- Breastfeeding is protective against giardiasis in nursing infants in endemic areas

- Zinc and vitamin A supplementation is associated with a protective effect in children

3.8.3.2 Cholera (አተት፣ ኮሌራ)

- A toxin-mediated acute diarrhoeal disease characterized by **profuse diarrhea and dehydration/ shock** that can cause death in a few hours.
- Can occur in **endemic** (usually children) or **epidemic forms** (all age groups)
- May be fatal in less than 24 hours
- Caused by Vibrio cholerae: — Produces cholera toxin (responsible for the clinical presentation

Pathogenesis

- Ingestion of V. cholerae through contaminated water or food or through direct person-to-person contact →(must) survive the gastric acidic pH → colonize the small intestine → produce cholera toxin → massive secretory diarrhea → loss of fluid, Na+, Cl-, HCO2- and K

Epidemiology

Mainly occurs in settings where

- Limited access to clean water
- Flooding during rainy seasons
- Resource-limited settings
- Migrant camps

Clinical manifestations

- IP: 1 to 2 days
- Mild disease: loose stool or watery diarrhea
- Severe disease ("cholera gravis"): The diarrhoea is classically voluminous/ profuse (up to 1L/hr)/, non-offensive, and somewhat looks gray or **"rice-water" diarrhea** with flecks of mucous
- Fever is absent.
- **Dehydration, shock, electrolyte imbalance**
- Usually: no pain, no tenesmus, no blood in stool, no fever

Mortality from cholera

- May reach 50 to 70% in untreated patients
- Reduced to less than 1% with just appropriate rehydration

Diagnosis

- Presumptive diagnosis clinically made in patients with severe acute watery diarrhea
- Dx is confirmed by stool culture (specific selective media)
- Rapid tests: stool dipsticks, dark field microscopy.

Management

- Non pharmacologic
  - advise patients to take fluid
  - Symptomatic/Supportive Treatment
- For dehydration in mild cases give ORS, PRN and IV fluid for severe DHN
- Treat shock, electrolyte imbalance; KCl solution 20-40mmol/liter may be added as required

Pharmacologic

Look at table below

Prevention:

- The promotion of adequate hygienic conditions in the community is important to prevent an outbreak and spread of the disease.

Table -Treatment of common Infectious Diarrheal Disease

Type of diarrhoeal disease (aetiology);		**Management**
Bacillary dysentery	**Microorganism**	**First line treatment options**
	E.coli	✓ Ciprofloxacin, 500mg, PO, BID for 3 days
	Shigella spp.	✓ Ciprofloxacin, 500mg, PO, BID for 3 days or ✓ Azithromycin 500mg, PO, daily for 3 days
	Salmonella (non-typhoidal)	Gastroenteritis: ✓ Ciprofloxacin, 500mg, PO, BID for 5-7 days or ✓ Azithromycin 1g, po, daily for 4days (1g on 1st day then, 500mg, PO, daily for 6 days) if Bacteremia: ✓ ceftriaxone 1g IV BID for 7-10 days
	Campylobacter	✓ Macrolides / fluoroquinolone for 5 days
	Yersinia species (rare, if identified)	Enterocolitis (mild): ✓ no treatment benefit or some benefit form Ciprofloxacin 500mg, PO, BID for 5 days Bacteremia: ✓ Ceftriaxone 1g IV, BID for 3 weeks PLUS

		✓ gentamycin 5mg/kg/day, IV, TID for 3 weeks ☛ change IV to PO once the pt is stable.
	Special population considerations **Pregnant women:** ✓ Third generation cephalosporins should be used in pregnant mothers in place of fluoroquinolone or azithromycin.	
Amoebiasis **(Entamoeba dispar, Entamoeba histolytica)**		✚ Treatment of invasive colitis consists of a tissue agent (e.g metronidazole) followed by a luminal (e.g. parmomycin) agent to eliminate intraluminal cysts. ✚ Intraluminal infection can be treated with one of the luminal agents. **First line** ✓ **Metronidazole**, 500-750mg P.O., TID for 5-7 days. ➢ For children: 7.5mg/kg/dose, P.O., TID for 5-7 days. **Alternative** ✓ **Tinidazole**, 2g P.O. daily for 3 consecutive days. ➢ For children: 50-60mg/kg daily for 3 days **Eradication of cysts** **First line** ✓ **Diloxanide Furoate**, 500mg, PO, TID, for 10 days. course may be repeated if necessary. Or ➢ Child over 25kg, 20mg/kg/day, TID, for 10 days; ✓ **Paromomycin**, 25 - 35mg/kg/day, P.O, TID, for 7 days Or ✓ **Iodoquinol (Diiodohydroxyquin):** 650 mg, PO, TID for 20 days ➢ for children 30 - 40 mg/kg/day, TID, for 20 days **Special population considerations → Pregnant women:** ✓ For mild to moderate amoebic colitis **paromomycin is preferred.** ✓ **For severe amoebic colitis treatment with metronidazole is preferred over paromomycin.** **Caution:** no well controlled studies demonstrating safety of metronidazole in

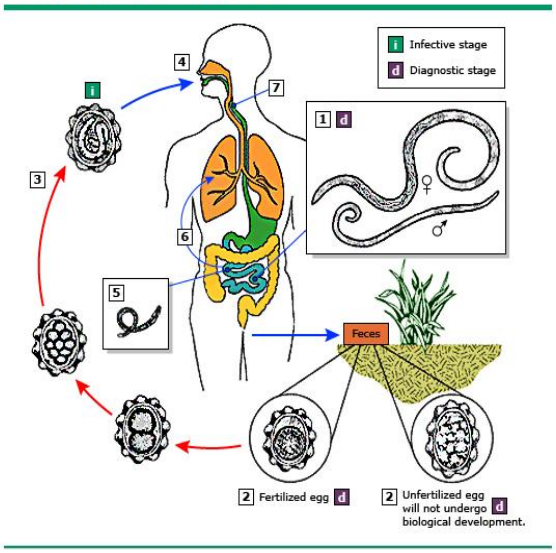
	pregnancy; thus, use should be limited for sever cases.
Giardiasis (*Giardia lamblia)*	✚ Asymptomatic cases usually resolve without treatment without any complication. **For symptomatic patients** **first line** ✓ **tinidazole,** 2 g, PO, stat **Alternatives** ✓ **Metronidazole**, 250-500mg P.O., TID for 5 days or ✓ **Albendazole**, 400 mg, PO, daily for 5 days or ✓ **Nitazoxanide**, 500 mg, PO, BID, for 3 days **For pregnant women** ✓ with mild giardiasis, treatment might be **delayed until at least the 2nd trimester** if patient is able to maintain hydration and nutrition. ✓ If treatment is mandatory during the **1st trimester**, **paromomycin** 10 mg/kg, PO, TID, for 5 to 10 days should be used22. Paromomycin has a limited systemic absorption. ✓ During the 2nd **and 3rd trimesters, paromomycin, tinidazole, nitazoxanide, or metronidazole** can be used as an alternative.
Cholera (Vibrio cholerae)	**First line** ✓ Doxycycline, 100mg, P.O., BID for 3 days. ▪ For children: 6mg/kg daily for 3 days **Alternatives** ✓ Tetracycline, 500mg P.O., QID for 3-5 days. OR ✓ cotrimoxazole 960mg P.O., BID for 5 days (i.e. Sulfamethoxazole+trimethoprim, 800mg/160mg) OR ✓ Ciprofloxacin, 500mg P.O., BID, for 3-5 days.

3.8.2 Intestinal Helminthic Infestations (የአንጀት ጥገኛ ተውሳክ ፤የአንጀት ትላትል) *and blood flukes*

3.8.2.1 Ascariasis/Round worm/ (ወስፋት)

- Ascariasis is one of the most common helminthic human infections worldwide.

Ascaris lumbricoides life cycle



Adult worms (females 20 to 35 cm; males 15 to 30 cm) **(1)** live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces **(2)**. Unfertilized eggs may be ingested but are not infective. Fertile eggs embryonate and become infective after 18 days to several weeks **(3)**, depending on the environmental conditions (optimum: moist, warm, shaded soil). After infective eggs are swallowed **(4)**, the larvae hatch **(5)**, invade the intestinal mucosa, and are carried via the portal, then systemic circulation to the lungs **(6)**. The larvae mature further in the lungs (10 to 14 days), penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed **(7)**. Upon reaching the small intestine, they develop into adult worms **(1)**. Between two and three months are required from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live one to two years.

Transmission

- Ascariasis is transmitted via ingestion of food or water contaminated with eggs of A. lumbricoides.
- Also, transmission can occur when eggs are taken with dust in the environment.
- Asymptomatically infected children are the main sources of continued transmission of the diseases.

Clinical Manifestations

- ✓ Most people with ascariasis are asymptomatic
- ✓ Only those with high worm burden exhibit clinical features of the diseases.

Intestinal Manifestations:

- ✓ Abdominal discomfort; anorexia; nausea; diarrhea

- ✓ Growth retardation and malnutrition; steatorrhea and malabsorption
- ✓ Worms may obstruct lumen and cause intestinal obstruction
- ✓ Biliary migration of worms may cause abdominal pain, cholecystitis, cholangitis, obstructive jaundice

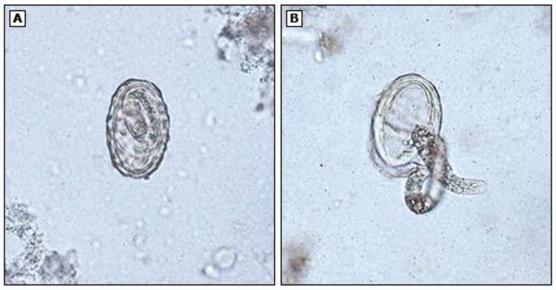
Pulmonary Manifestations:

- ✓ Transient respiratory symptoms during migration through the lungs
- ✓ Rare in area where transmission is common
- ✓ Symptoms of **Loeffler's Syndrome** 1-2 weeks after ingestion of eggs
- ✓ Low grade fever, dry cough, burning substernal discomfort, sometimes dyspnea and blood tinged sputum
- ✓ Urticaria in about 15% of the cases
- ✓ Infiltrates on chest X ray;
- ✓ blood eosinophilia
- ✓ Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts.

Diagnosis

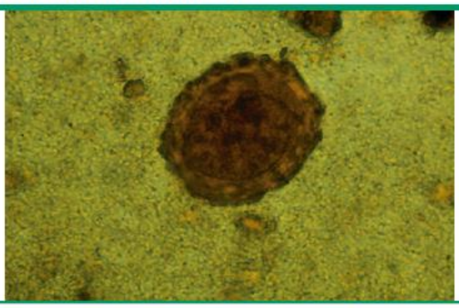
- ❖ Stool microscopy shows characteristic eggs.
- ❖ Sometimes, adult worms may be passed with the feces and confirm diagnosis; they may also be vomited out, coughed up
- ❖ During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool

Larvae of *Ascaris lumbricoides* hatching from eggs



Larva of *A. lumbricoides* hatching from an egg.

***Ascaris lumbricoides* in stool**



Wet mount of stool (x400) showing the ovum of *Ascaris lumbricoides*.

Treatment

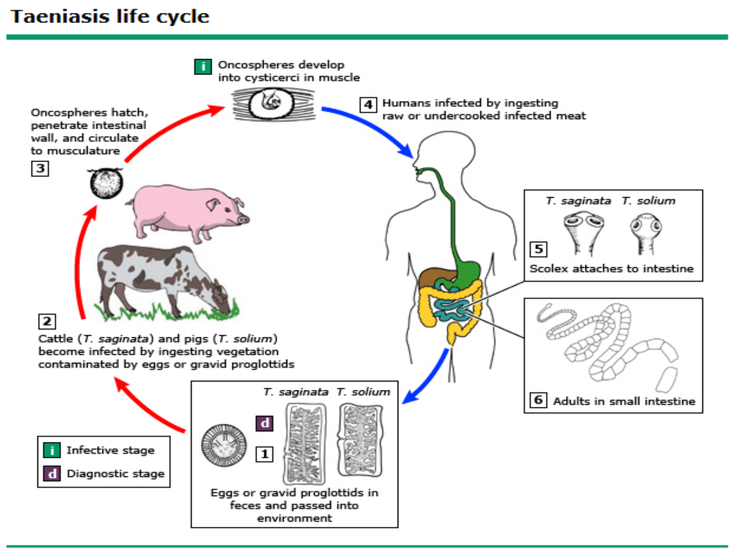
Look at table below

Follow-up

- Follow with repeat S/E after 2-3 months, and those +ve for eggs should get repeat treatment.

3.8.2.2 Taeniasis/Tape worm/ (ኮሶ)

- There are two main species of *Taenia* for which humans are the only definitive hosts. These are
  1. *Taenia saginata* /beef tapeworm/ and
  2. *Taenia solium* /pork tapeworm/.
- *T. saginata* occurs worldwide but is most common in areas where consumption of undercooked beef is customary, such as Europe and parts of Asia.
- The third species, *T. asiatica*, is found among pigs in some places.
- Concurrent infections with more than one *Taenia* species have been described.


Taeniasis life cycle
i Oncospheres develop into cysticerci in muscle
4 Humans infected by ingesting raw or undercooked infected meat
Oncospheres hatch, penetrate intestinal wall, and circulate to musculature
3
T. saginata T. solium
5 Scolex attaches to intestine
6 Adults in small intestine
2 Cattle (T. saginata) and pigs (T. solium) become infected by ingesting vegetation contaminated by eggs or gravid proglottids
T. saginata T. solium
d
1
Eggs or gravid proglottids in feces and passed into environment
i Infective stage
d Diagnostic stage

Figure; Taeniasis is the infection of humans with the adult tapeworm of *Taenia saginata*, *T. solium*, or *T. asiatica*. Humans are the only definitive hosts for these three species. Eggs or gravid proglottids are passed with feces **(1)**; the eggs can survive for days to months in the environment. Cattle (*T. saginata*) and pigs (*T. solium* and *T. asiatica*) become infected by ingesting vegetation contaminated with eggs or gravid proglottids **(2)**. In the animal's intestine, the oncospheres hatch **(3)**, invade the intestinal wall, and migrate to the striated muscles, where they develop into cysticerci. A cysticercus can survive for several years in the animal. Humans become infected by ingesting raw or undercooked infected meat **(4)**. In the human intestine, the cysticercus develops over two months into an adult tapeworm, which can survive for years. The adult tapeworms attach to the small intestine by their scolex **(5)** and reside in the small intestine **(6)**. Length of adult worms is usually 5 m or less for *T. saginata* (however it may reach up to 25 m) and 2 to 7 m for *T. solium*. The adults produce proglottids that mature, become gravid, detach from the tapeworm, and migrate to the anus or are passed in the stool (approximately six per day). *T. saginata* adults usually have 1000 to 2000 proglottids, while *T. solium* adults have an average of 1000 proglottids. The eggs contained in the gravid proglottids are released after the proglottids are passed with the feces. *T. saginata* may produce up to 100,000 and *T. solium* may produce 50,000 eggs per proglottid, respectively.

Clinical manifestations

- Most human carriers of adult tapeworms are asymptomatic.
- Intermittently, patients may pass proglottids in the stool (*T. solium*) or spontaneously (*T. saginata*) or may notice segments in their stool or sense the movement of proglottids through the anus.
- There may be associated symptoms including nausea, anorexia, or epigastric pain.
- Anxiety, headache, dizziness, and urticaria can also occur. A peripheral eosinophilia (up 15 percent) may be observed.
- Occasionally, segments can enter the appendix, common bile duct, or pancreatic duct and cause obstruction.
- Rarely, proglottids can be aspirated or regurgitated.

Diagnosis

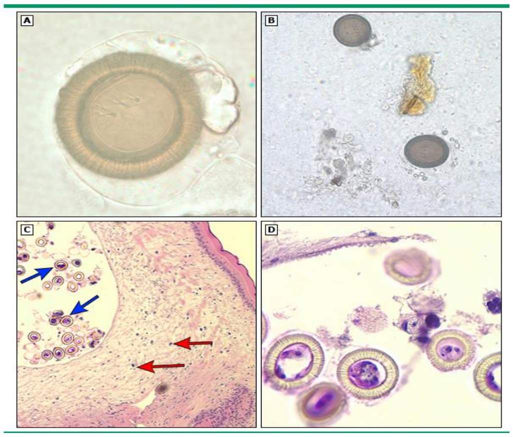
1. microscopy

- The diagnosis is generally established by identifying eggs or proglottids in the stool.

- The eggs of *Taenia* species are morphologically indistinguishable
- they are round with a double-walled, radially striated membrane and measure 30 to 40 micrometers. *T. saginata* eggs have an acid-fast shell; *T. solium* eggs are not acid fast (picture 1).
- The proglottids and scolices of *T. solium* and *T. saginata* are morphologically distinguishable and can be used to establish a species diagnosis (picture 2). The *T. saginata* proglottids have 12 or more primary uterine branches; *T. solium* proglottids have ≤10. These branches can be seen on direct examination or by injecting India ink into the segment via its lateral genital opening.
- The scolex usually remains in the intestine when proglottids are passed; it is rare for the entire worm to be eliminated spontaneously. Following antiparasitic therapy, however, the scolex of a fully evacuated worm may be identified in the stool. *T. saginata* has a scolex with four lateral suckers and no hooks ("unarmed"). *T. solium* has a scolex with a well-developed rostellum (crown) that has four suckers and a double row of hooks ("armed").

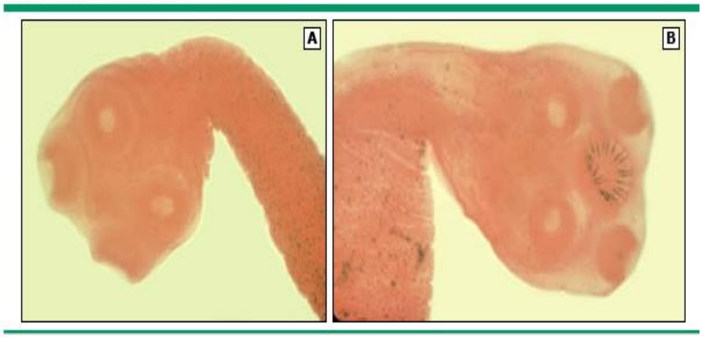
2. **Immunologic and molecular methods; ELISA, PCR**
3. **visualizing the worm on capsule endoscopy**

Taeniasis eggs



Picture 1 (A, B) *Taenia* spp eggs in unstained wet mounts. Four hooks can clearly be seen in figure A.
(C) Cross-section of a proglottid of *Taenia* spp, stained with hematoxylin and eosin (H&E). Note the thick outer tegument and the loose parenchyma filling the body. Calcareous corpuscles (red arrows), characteristic of the cestodes, can be seen in the parenchyma. Eggs (blue arrows) can also be seen.
(D) Higher magnification of figure C showing a close-up of the eggs. Note the characteristic striations, typical for the taeniids. Not visible in these images are the hooks commonly seen in cestode eggs. Hooks do not stain with H&E but are refractile and visible with fine focusing of the microscope.

Taenia scolices



(A) Scolex of *T. saginata*. Note the four large suckers and lack of rostellum and rostellar hooks.
(B) Scolex of *T. solium*. Note the four large suckers and rostellum containing two rows of hooks.

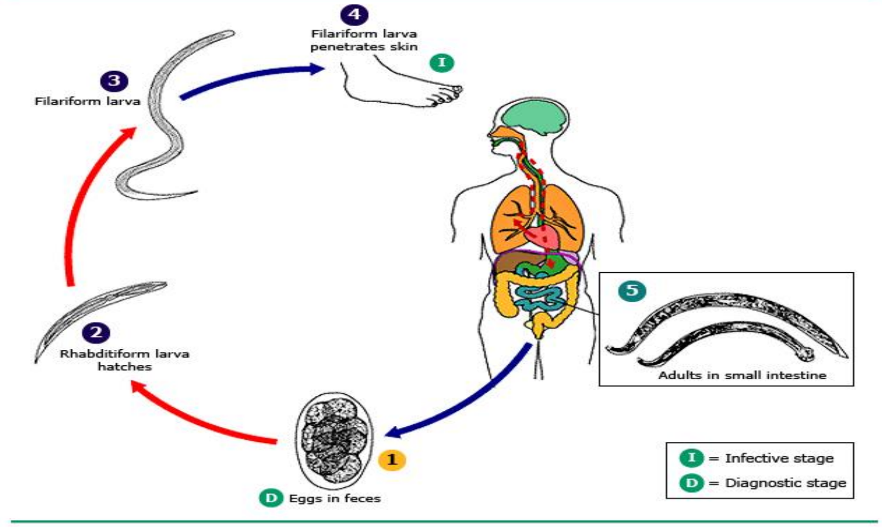
Picture 2

Treatment

Look at table below

3.8.2.3 Hook worm (መንጠቆ)

- Two common species: Necator americanus and Ancylostoma duodenale
- More prevalent in resource-poor countries in the tropics.
- Hookworm disease develops from a combination of factors
  - a heavy worm burden;
  - a prolonged duration of infection; and
  - an inadequate iron intake
- results in iron deficiency anemia and, on occasion, hypoproteinemia



Intestinal hookworm infection life cycle

4
Filariform larva penetrates skin
I
3
Filariform larva
5
Adults in small intestine
2
Rhabditiform larva hatches
1
D Eggs in feces
I = Infective stage
D = Diagnostic stage

Eggs are passed in the stool **(1)**, and under favorable conditions (moisture, warmth, shade) larvae hatch in one to two days. The released rhabditiform larvae grow in the feces and/or the soil **(2)**, and after 5 to 10 days (and two molts) they become filariform (third-stage) larvae that are infective **(3)**. These infective larvae can survive three to four weeks in favorable environmental conditions. On contact with the human host, the larvae penetrate the skin and are carried through the blood vessels to the heart and then to the lungs. They penetrate into the pulmonary alveoli, ascend the bronchial tree to the pharynx, and are swallowed **(4)**. The larvae reach the small intestine, where they reside and mature into adults. Adult worms live in the lumen of the small intestine, where they attach to the intestinal wall with resultant blood loss by the host **(5)**. Most adult worms are eliminated in one to two years, but the longevity may reach several years. Some *Ancylostoma duodenale* larvae, following penetration of the host skin, can become dormant (in the intestine or muscle). In addition, infection by *A. duodenale* may probably also occur by the oral and transmammary route. *Necator americanus*, however, requires a transpulmonary migration phase.

Clinical Manifestations

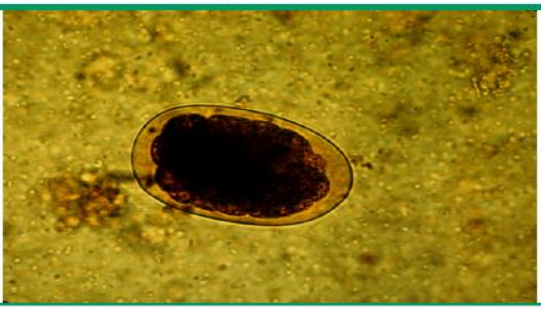
- Most people who are infected with hookworm are asymptomatic.
- Some may develop **pruritic maculopapular rash at the site of skin penetration.**
- Serpiginous tracks of subcutaneous migration might be seen in previously sensitized patients.
- Mild transient features of pneumonitis can be seen when worms migrate through the lungs.
- In the **early** intestinal phase of infection, patients may have abdominal manifestations including **abdominal discomfort, nausea, vomiting, diarrhea**, etc.
- The **major consequence** of chronic hookworm infection is **iron-deficiency anemia.**

Diagnosis

- ✓ Diagnosis is established by demonstrating the characteristic oval eggs.

- ✓ In addition, patients will have iron deficiency anemia and eosinophilia.

Hookworm ovum in stool



A wet mount of stool (x400) shows an ovum of hookworm. The eggs of the two species of hookworm, *Necator americanus* and *Ancylostoma duodenale*, are indistinguishable in wet mounts.

Treatment

- ✓ Look at table below

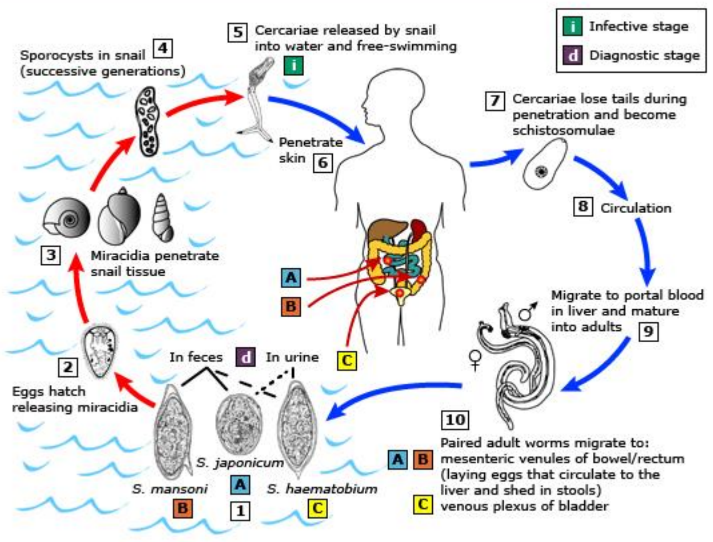
Prevention

- ☛ Improved environmental sanitation and the use of latrines and public health education.
- ☛ Wearing shoes is also found to prevent infection.

3.8.2.4 Schistosomiasis (ቢሊሃርዚያ)

- Schistosomiasis is a disease caused by infection with parasitic blood flukes. It is also known as "bilharziasis" after Theodor Bilharz
- ❖ 5 species of the parasitic trematode genus *Schistosoma* can cause infection in humans
    - ➢ the intestinal species → ***S. mansoni***, ***S. japonicum***, *S. mekongi*, and *S. intercalatum* and
    - ➢ the urinary species→ ***S. haematobium***
    - ➢ The three major species are *Schistosoma mansoni* (Africa and South America), *S. japonicum* (East Asia), and *S. haematobium* (Africa and Middle East)

Life cycle of schistosomiasis


i Infective stage
d Diagnostic stage
4 Sporocysts in snail (successive generations)
5 Cercariae released by snail into water and free-swimming
i
Penetrate skin 6
7 Cercariae lose tails during penetration and become schistosomulae
8 Circulation
Migrate to portal blood in liver and mature into adults 9
♂
♀
3 Miracidia penetrate snail tissue
A
B
C
2 Eggs hatch releasing miracidia
In feces
d
In urine
S. japonicum
S. mansoni
S. haematobium
A
B
1
C
10 Paired adult worms migrate to:
A B mesenteric venules of bowel/rectum (laying eggs that circulate to the liver and shed in stools)
C venous plexus of bladder

Life cycle: Eggs are eliminated with feces or urine **(1)**. Under optimal conditions, the eggs hatch and release miracidia **(2)**, which swim and penetrate specific snail intermediate hosts **(3)**. The stages in the snail include two generations of sporocysts **(4)** and the production of cercariae **(5)**. Upon release from the snail, the infective cercariae swim, penetrate the skin of the human host **(6)**, and shed their forked tail, becoming schistosomulae **(7)**. The schistosomulae migrate through several tissues and stages to their residence in the veins **(8,9)**. Adult worms in humans reside in the mesenteric venules in various locations, which at times seem to be specific for each species **(10)**. For instance, *S. japonicum* is more frequently found in the superior mesenteric veins draining the small intestine **(A)**, and *S. mansoni* occurs more often in the superior mesenteric veins draining the large intestine **(B)**. However, both species can occupy either location, and they are capable of moving between sites, so it is not possible to state unequivocally that one species only occurs in one location. *S. haematobium* most often occurs in the venous plexus of bladder **(C)**, but it can also be found in the rectal venules. The females (size 7 to 20 mm; males slightly smaller) deposit eggs in the small venules of the portal and perivesical systems. The eggs are moved progressively toward the lumen of the intestine (*S. mansoni* and *S. japonicum*) and of the bladder and ureters (*S. haematobium*), and are eliminated with feces or urine, respectively **(1)**.

Clinical Features

- manifestations of schistosomiasis occur in three stages which vary by species, by intensity of infection and other host factors, such as age and genetics.

1. **swimmers' itch**
    - ✓ During the phase of cercarial invasion, a form of dermatitis occurs most often with *S. mansoni* and *S. japonicum* infections,
    - ✓ manifesting 2 or 3 days after invasion as an **itchy maculopapular rash** on the affected areas of the skin.
    - ✓ severe when humans are exposed to avian schistosomes.
    - ✓ is a self-limiting clinical entity

2. **acute schistosomiasis or Katayama fever**

- ✓ It is a systemic hypersensitivity reaction to schistosome antigens and circulating immune complexes.
- ✓ The complex occurs during worm maturation and at the beginning of oviposition (i.e., 4—8 weeks after skin invasion)
- ✓ **a serum sickness—like syndrome with fever, generalized LAP, and hepatosplenomegaly**
- ✓ high degree of peripheral-blood **eosinophilia.**
- ✓ Parasite-specific antibodies may be detected before schistosome eggs are identified in excreta
- ✓ generally benign

3. **chronic schistosomiasis**

- ☛ **intestinal schistosomiasis**
  - ☛ may begin a few months after infection and may last for years
  - ☛ colicky abdominal pain, bloody diarrhea, and anemia.
  - ☛ fatigue and an inability to perform daily routine functions
  - ☛ growth retardation.
  - ☛ The severity of intestinal schistosomiasis is often related to the intensity of the worm burden
  - ☛ colonic polyposis
- ☛ **Hepatosplenic schistosomiasis (HSS)**
  - ☛ Hepatomegaly
    - ▪ in 15—20% of infected individuals;
    - ▪ correlates roughly with intensity of infection,
    - ▪ occurs more often in children, and
    - ▪ may be related to specific HLA haplotypes
    - ▪ right-upper-quadrant "dragging" pain
  - ☛ Portal hypertension with splenomegaly and varices
  - ☛ Liver fibrosis
    - ▪ In late-stage disease
    - ▪ liver function deterioration
    - ▪ ascites, hypoalbuminemia, and defects in coagulation
- ☛ **Urinary schistosomiasis**
  - ☛ 80% have dysuria, frequency, and hematuria
  - ☛ Urine examination
    - ▪ blood and albumin
    - ▪ high frequency of bacterial urinary tract infection and

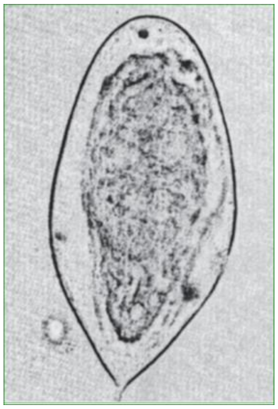
- ✓ urinary sediment cellular metaplasia

  - ☛ hydroureter and hydronephrosis (25—50%)
  - ☛ bladder granulomas undergo fibrosis
    - ▪ squamous cell carcinoma of the bladder
- ☛ **pulmonary schistosomiasis**

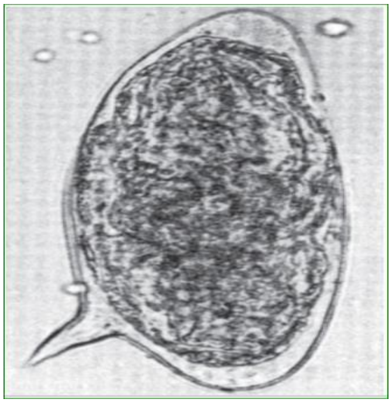
    - embolized eggs lodge in small arterioles, producing acute necrotizing arteriolitis and granuloma formation.
  - eggs reach the lungs after the development of portosystemic collateral circulation or via connections between the vesical and systemic circulation.
  - Subsequent fibrous tissue deposition leads to endarteritis obliterans, pulmonary hypertension, and cor pulmonale.
- **CNS schistosomiasis (Neuroschistosomiasis)**
  - Adult worms' embolization to the spinal cord or cerebral microcirculation, release eggs and cause intense inflammatory reaction with local tissue destruction and scarring to that result in cerebral disease or myelopathy. Hence, if neuroschistosomiasis is confirmed or suspected but not proven, corticosteroid therapy should be administered
  - Epilepsy
    - *S. japonicum*
    - Migratory worms deposit eggs in the brain and induce a granulomatous response
    - transverse myelitis
    - *S. mansoni* and *S. haematobium*
    - due to eggs traveling to the venous plexus around the spinal cord

Diagnosis

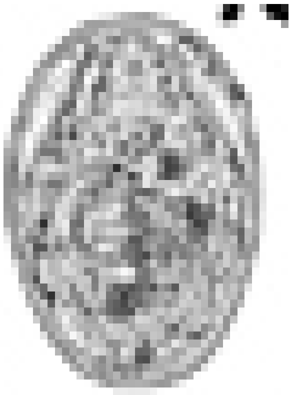
- Microscopy
  - ✓ Identification of schistosome eggs in a stool or urine sample via microscopy is the **gold standard** for the diagnosis of schistosomiasis.
  - ✓ It can also be used for species identification and to measure the parasite burden
  - ✓ Eggs of *S. mansoni*, *S. japonicum*, *S. haematobium*, *S. mekongi*, and *S. intercalatum* can be found in stool (although *S. haematobium* is principally found in urine).
  - ✓ In endemic settings, the **Kato-Katz method** is a common thick-smear technique using 5 mg of stool examined with a low-power microscope lens



S. hematobium

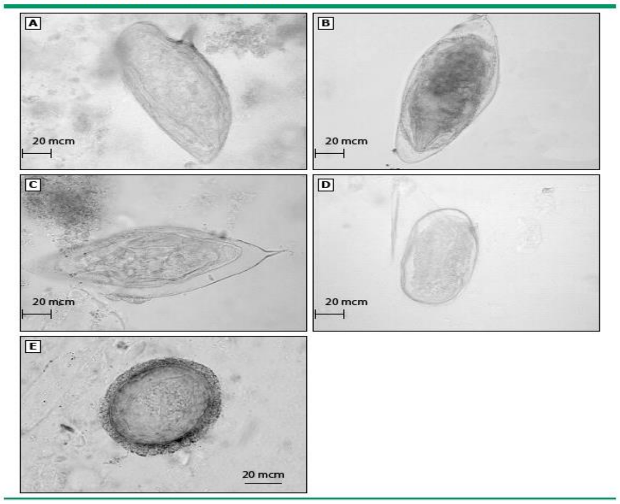


S. mansoni



S. japonicum

Schistosomiasis egg morphology



Human schistosomiasis eggs: (A) *S. mansoni*. (B) *S. hematobium*. (C) *S. intercalatum*. (D) *S. japonicum*. (E) *S. mekongi*.

- **cercarial dermatitis** → History
- **Katayama fever**
  - ✓ high-level peripheral-blood eosinophilia, and
  - ✓ a positive serologic assay for schistosomal antibodies
    - FAST-ELISA and the confirmatory enzyme-linked immune electrotransfer blot (EITB).
    - Both tests are highly sensitive and 96% specific.
    - In some instances, examination of stool or urine for ova may yield positive results.
- **Established infection**
  - ✓ presence of schistosome ova in excreta
  - ✓ Stool examination by the kato thick smear
  - ✓ Urine examination by microscopy of sediment or by filtration of a known volume through nuclepore filters.

    - Kato thick smear and nuclepore filtration Provide quantitative data on the intensity of infection to assess the degree of tissue damage and to monitor the effect of chemotherapy
- ✓ Rectal biopsies; other biopsy procedures (e.g, Liver biopsy) are not needed, except in rare circumstances.

Treatment of Schistosomiasis

☛ Look at table below

- ❖ **cercarial dermatitis**
  - ○ Antipruritic agents
- ❖ **acute schistosomiasis or Katayama fever**
  - ○ Initial management: corticosteroids (prednisolone 20 - 40 mg daily for 5 days).
  - ○ Praziquantel should be initiated only after acute symptoms have resolved and should be administered concomitantly with corticosteroids
- ❖ **Neuroschistosomiasis**
  - ✓ **prednisone** 1 to 2 mg/kg for 2 weeks to six months → to prevent irreversible tissue damage.
    - ♥ In settings of long-term corticosteroid use strongyloidiasis should be excluded.
  - ✓ **Praziquantel**, 40 mg/kg stat, a few days after (to reduce paradoxical worsening of neurologic symptoms) initiation of corticosteroid treatment
  - ✓ The two therapies (prednisolone and praziquantel) should be given concomitantly.
- ❖ For all individuals with established infection, treatment to eradicate the parasite should be administered (table below).
- ❖ Hepatomegaly and bladder lesions regress with early treatment but established fibrosis persists

Monitoring (follow up)

Follow-up after treatment includes:

- Monitoring of **clinical manifestations**,
  - ✓ Eosinophilia → initial elevations are likely. Eosinophilia persisting for > 3 months after therapy may reflect insufficient drop of parasite burden and/or an additional helminth infection.

- **Microscopy** for eggs in **stool or urine**
    - ✓ **no sooner than 6 weeks in endemic areas** following treatment and 3 - 6 months after treatment in nonendemic areas.
    - ✓ Persistence of viable eggs after 6 to 12 weeks after initial of therapy warrants repeat treatment with praziquantel (40 to 60 mg/kg in two divided doses as in the initial therapy).
- Medical imaging (**abdominal ultrasound or MRI**)
    - ✓ to document long-term reversal of urinary tract lesions or periportal liver disease after repeated mass treatment.

Prevention

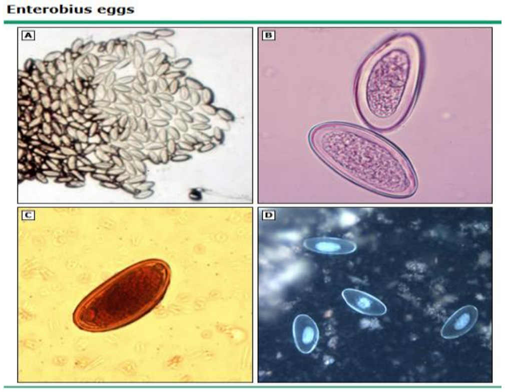
Control strategies for Schistosomiasis endemic areas include:

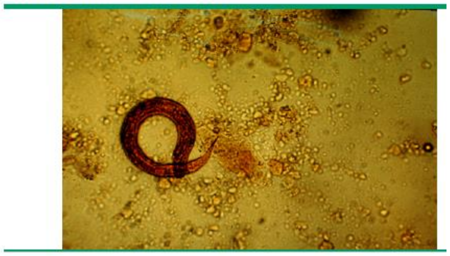
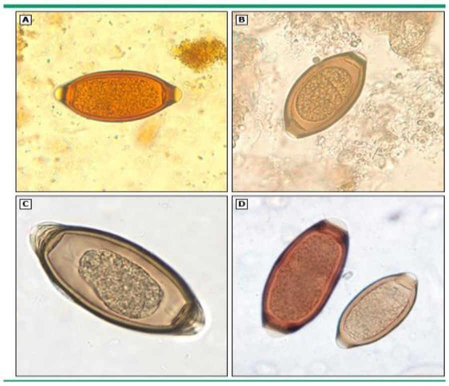
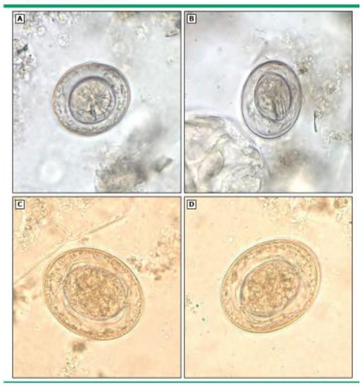
- ☛ Water sanitation programs:
    - ✓ safe water supplies with proper sewage control,
    - ✓ Minimizing contact with fresh water or wearing protective clothing and footwear in location of freshwater contact,
    - ✓ Vigorous toweling of exposed skin and/or applying insect repellent DEET (N,N-diethyl-mtoluamide) after exposure to fresh water.
- ☛ Mass drug administration (MDA):
    - ✓ praziquantel (nonpregnant and pregnant adults, and children ≥4 years: 40 mg/kg orally once; contraindicated in children <4 years).
    - ✓ Annually repeated MDA is appropriate, but, more frequent administration may induce resistance in endemic areas.
- ☛ no vaccine against schistosomiasis
- ☛ Skin topical agents
- ☛ Molluscicides — eg. Lemma toxin (Aklilu Lemma from endod)
- ☛ Follow up of exposed individuals

Table -Treatment of common intestinal helminthic parasitic infestations and blood flukes

Scientific name of the parasite/common name/(aetiology); ✓ Mode of transmission and remarks	Management
Ascariasis/round worm/ (Ascaris lambricoids)	First line-options ✓ **Albendazole,** 400mg P.O. stat, ▪ for children: 1 — 2 years, 200mg stat.

✓ Ingestion of the larvae of the parasite together with food ✓ Presence of migrating larvae in the lungs can provoke pneumonia	✓ **Mebendazole,** 100mg P.O.BID for 3 days or 500mg, stat **Alternative (pregnant women)** ✓ **Pyrantel pamoate**, 700mg P.O. stat
Hookworm (Necator americanus or Ancylostoma duodenale) ✓ Penetration of the larvae of the parasite through skin	**First line**-options ✓ **Albendazole,** 400mg P.O. stat (**preferred**) **OR** ✓ **Mebendazole,** 100mg P.O. BID for 3 days or 500mg stat **Alternatives:** ✓ **Pyrantel pamoate**, 700mg P.O. stat
Taeniasis/tape worm/ (T. saginata, T.solium) ✓ Ingestion of row meat or milk from cows and pork ✓ *T. solium* (pork tapeworm) may cause fatal cysticercosis ✓ *T.saginata is known as beef tape worm*	**First line-Intestinal infestation** ✓ **Praziquantel** P.O. 600mg or 10mg/Kg, stat **Alternative** ✓ **Niclosamide,** 2g, P.O. stat **Treatment of neurocysticercosis** ✓ **Albendazole** P.O. 15mg/kg/day for 8- 28 days **or** ✓ **Praziquantel,** 50—100mg/kg/day, TID, for 15—30 days. ▪ Longer courses are often needed in patients with multiple subarachnoid cysticerci **PLUS** ✓ High-dose glucocorticoids ✓ Anti-epileptics (if there is seizure)
Shistosomiasis / bilharziasis/	**First line** **For S.mansoni, S. hematobium,** S. intercalatum ✓ **Praziquantel**, 40 mg/kg stat or in 2 divided doses 4-6 hours apart on 1 day **For S. japonicum**, S. makongi ✓ **Praziquantel**, 60 mg/kg in 2 divided doses 4-6 hours apart on 1 day. ☛ **Repeated treatment is usually required in endemic areas** ☛ Praziquantel is not effective against the larval - thus **treatment is most effective from 4-6 weeks after exposure**, as infection well established and worms fully matured. **Alternatives** **For S. haematobium** ✓ **Metrifonate**, 600 mg P.O., TID at 14 days interval. **For S. mansoni** ✓ **Oxamniquine**, 1250 mg (30 mg/kg) P.O. stat. ☛ *It is contraindicated in pregnancy and in general is not as effective as praziquantel.* ✓ **Artemisinin** derivatives may be used in very early infection to disrupt the glucose metabolism of immature schistosomes.

	Considerations in special population **Pregnancy**: ✓ **Praziquantel** is pregnancy **category B**. Praziquantel is excrete in breast milk. Although no adverse effects during lactation have reported, termination of breastfeeding during treatment and for 72 hours thereafter or postponing treatment until after breastfeeding might be considered. ✓ **Oxamniquine is contraindicated** in pregnancy. **Pediatrics:** ✓ divided dosing is preferred than single dose in children and infants (20 mg/kg/dose two to three times daily for 1 day)
Enterobiasis/pin worm/ (Enterobius Vermicularis) ✓ Ingestion of the eggs of the parasite together with food ✓ Common in children and auto infection may occur  (A) Eggs of *E. vermicularis* in a cellulose-tape preparation, (B) in a wet mount, (C) in an iodine-stained wet mount from a formalin concentrate, (D) viewed under UV microscopy.	First line-options ✓ **Mebendazole,** 100mg P.O. BID for 3 days, repeat in 2 weeks OR ✓ **Albendazole,** 400mg P.O. stat, repeat in 2 weeks, Alternative ✓ **Piperazine,** 4g po, stat. ☛ Simultaneous treatment of the entire household is warranted due to high transmission possibilities
Strongyloidiasis/Thread worm/ (Strongloidexs stercolaries) ✓ Penetration of the larvae of the parasite through skin ✓ Larvae migrate to the lungs where they cause tissue destruction and bleeding. ✓ Treat concomitant anaemia if any	First line ✓ **Ivermectin,** 200μg/kg daily for 2 days. ✓ For disseminated strongyloidiasis, treatment with ivermectin should be extended for at least 5—7 days or until the parasites are eradicated. Alternatives-options ✓ **Thiabendazole,** 1500mg, P.O. BID, for 3 consecutive days **(comparable efficacy to ivermectin**). OR ▪ for children: 25mg/kg p.o. for 3 consecutive days ✓ **Albendazole** 400mg P.O.BID for 3 consecutive days (less effective than ivermectin).

Strongyloides stercoralis  Wet mount of stool (x100) shows the diagnostic larval form of *Strongyloides stercoralis*.	
Trichuriasis /whip worm/ (T.tricura) ✓ Heavy infestation leads to bloody diarrhoea, bleeding & weakness **Trichuriasis eggs**  (A) Egg of *T. trichiura* in an iodine-stained wet mount, (B) unstained wet mount, (C) unstained wet mount,(D) Two eggs of *T. trichiura*, showing the variability in size of the species.	**First line-options** ✓ **Mebendazole**, 500mg P.O., stat **(preferred over Albendazole)** OR ✓ **Albendazole,** 400mg, P.O. for 3 days ☛ **oxantel pamoate 15 to 30 mg/kg (if available) plus albendazole 400 mg on consecutive days is superior than other therapies**
Hymenolepis nana /dwarf tapeworm/ *Hymenolepis nana eggs*  (A-D) Eggs of *Hymenolepis nana*. On the inner membrane are two poles, from which four to eight polar filaments spread out between the two membranes. The oncosphere has six hooks.	**First line** ✓ **Praziquantel**, 25mg/kg or 1800mg P.O. stat, followed by repeat dose 10 days later **Alternatives** ✓ **Niclosamide,** 2g P.O. on the first day followed by 1g daily for 6 days

3.8.3 Dyspepsia, PUD and GERD (የጨጓራ ሕመም ፣ ቁስለትና አሲድ መብዛት)

3.8.3.1 Dyspepsia (የጨጓራ ሕመም፣ የምግብ አለመፈጨት ችግር)

- Dyspepsia is not a diagnosis by itself but it is a common symptom with an extensive differential diagnosis and a heterogeneous pathophysiology

Etiology

- Approximately 25 % of patients with dyspepsia have an underlying organic cause. However, **most commonly** (up to **75 %** of patients) have functional (idiopathic or non-ulcer) dyspepsia with **no underlying cause** on diagnostic evaluation
- Although there are several **organic causes for dyspepsia**, the main causes are**;**
  - ✓ **PUD (peptic ulcer disease)**
  - ✓ **GERD (gastroesophageal reflux disease),**
  - ✓ **NSAID-induced dyspepsia, and**
  - ✓ **Gastric malignancy**
- Medication (other than NSAID) induced dyspepsia, biliary pain, chronic abdominal wall pain and pancreatitis are other possible causes.

Clinical features

- Dyspepsia describes a wide and common clinical entity which presents in one of the three ways:
  1. Epigastric pain/burning (epigastric pain syndrome)
  2. Postprandial fullness
  3. Early satiety

ALARM SIGNS (need to be further investigation for cancer)

- Advanced age (>55years)
- Previous gastric surgery
- Unintended weight loss
- Persistent vomiting
- Hematemesis
- Progressive dysphagia/Odynophagia
- Otherwise unexplained anemia
- Palpable abdominal mass
- Lymphadenopathy
- Jaundice

Investigations

- ✓ H. Pylori test: IgG serology or stool antigen or 13C-urea test
  - ♥ H. Pylori test needs to be done for the following patients
    - ➢ Long standing dyspepsia
    - ➢ Younger than 55 year
    - ➢ No alarm symptoms
    - ➢ No use of NSAID
    - ➢ No features of GERD
  - ♥ "Test and treat" for H. Pylori can be practiced in these group of individuals
  - ♥ For more about H. Pylori test, click here → H. Pylori stool antigen and serum Ab test
- ✓ Hemoglobin/hematocrit
- ✓ Stool for occult blood → when indicated
- ✓ Upper GI endoscopy
  - ☛ Indication
    - ▪ Clinically significant weight loss (> 5% within 6 to 12 months)
    - ▪ Overt GI bleeding
    - ▪ > 1 alarm features
    - ▪ Rapidly progressive alarm features

Treatment

Non pharmacologic; recommend the following for patients with mild symptoms and no alarm signs

- Life style modification
  - ○ Dietary recommendations
    - ▪ Avoid offending foods/drinks → Dietary selection should not be forced or recommended universally unless patients identify the specific food item as triggering factor **(e.g. coffee/caffeine/, spicy foods, food with high fat content, carbonated beverages/ coca cola, mirinda, pepsi/, and chocolate).**
    - ▪ **Avoiding meals 2 -3 hours before bed** is also advisable.
    - ▪ Eat small amount of food frequently instead of eating much amount less frequently (e.g small amount of food 5 times daily instead of much amount 3 times daily)

        - Eat slowly during each feeding time
    - Weight loss in overweight and obsess patients.
    - Use pillows or head elevations to 15-20 cm during sleep.
    - Decrease or avoid alcohol
    - Stop smoking (for smokers)

Pharmacologic

I. H. Pylori negative

First line→ PPI

- ✓ Omeprazole, 20mg P.O., BID for 4-8 weeks
- ✓ Esomeprazole, 40mg P.O., daily for 4-8 weeks
- ✓ Pantoprazole, 40mg P.O., BID for 4-8 weeks

Alternatives → H2 receptor blockers

- ✓ Cimetidine, 400mg P.O., BID for 4-8 weeks
- ✓ Ranitidine, 150mg P.O. BID for 4-8 weeks
- ✓ Famotidine, 20-40mg P.O. daily for 4-8 weeks

II. H. Pylori positive: H. pylori eradication therapy

First line therapy → All drugs for 7-14 days

- ✓ Amoxicillin, 1gm, P.O. BID **PLUS**
- ✓ Clarithromycin, 500mg, P. O., BID **PLUS**
- ✓ PPI

Alternative (for penicillin allergic patients)→ All drugs for 7-14 days

- ♥ This regimen has a higher failure rate.
- ✓ Clarithromycin, 500mg P.O. BID PLUS
- ✓ Metronidazole, 500mg, P.O. BID **PLUS**
- ✓ PPI

- ➢ **For failure of triple therapy**, some physicians recommend **quadruple therapy** with bismuth added to the triple regimen → look at the algorism below
    - Amoxicillin, 1gm, P.O. BID **PLUS**
    - Clarithromycin, 500mg, P. O, BID **PLUS**
    - PPI **PLUS**
    - Bismuth, 2tab, PO, QID
- ➢ Serology tests for H. pylori shouldn't be used as a test of cure or eradication since they could remain positive for long period of time.

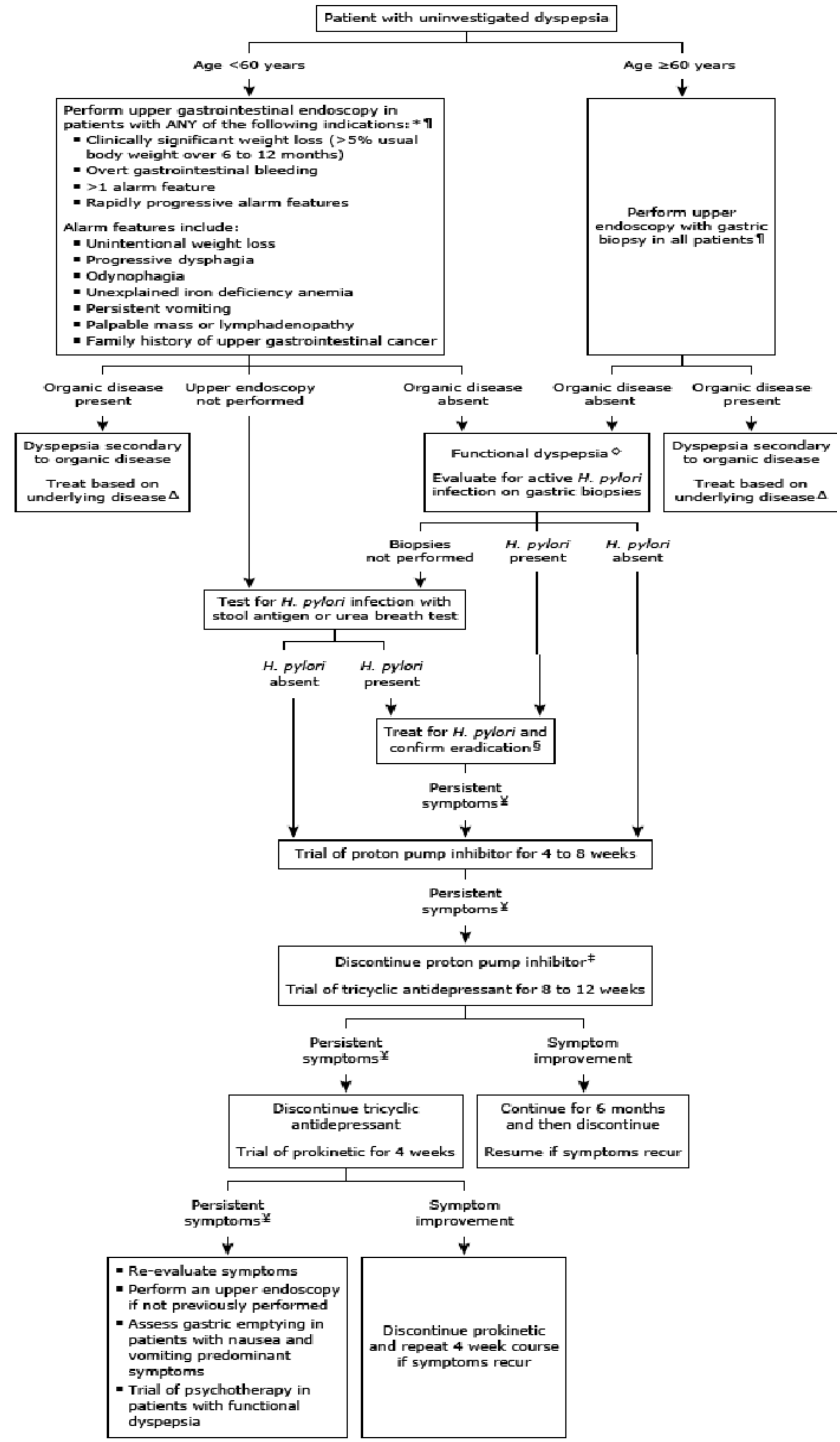
III. Antacids → for Symptomatic relief

- Antacids react with hydrochloric acid in the stomach to form salt and water which inhibits peptic activity by raising the Ph
- Magnesium antacids tend to be the best buffer
- **Maalox antacid syrup is available in most setups of Ethiopia → contains** Magnesium hydroxide and Aluminum hydroxide

Maalox Antacid
Maagpijn & Brandend maagzuur
250 ml
SANOFI

- ✓ Magnesium trisilicate + Aluminum hydroxide, 10-30ml, PO, PRN OR
- ✓ Magnesium hydroxide + Aluminum hydroxide, 10-30ml P.O. OR
- ✓ Magnesium trisilicate, 100-200mg, P.O. between meals PRN OR
- ✓ Magnesium hydroxide, 10-30ml or 600+622mg to 1200+1244mg, P.O between meals PRN

Approach to the evaluation and management of dyspepsia in adults


Patient with uninvestigated dyspepsia
Age <60 years
Age ≥60 years
Perform upper gastrointestinal endoscopy in patients with ANY of the following indications:*¶
▪ Clinically significant weight loss (>5% usual body weight over 6 to 12 months)
▪ Overt gastrointestinal bleeding
▪ >1 alarm feature
▪ Rapidly progressive alarm features
Alarm features include:
▪ Unintentional weight loss
▪ Progressive dysphagia
▪ Odynophagia
▪ Unexplained iron deficiency anemia
▪ Persistent vomiting
▪ Palpable mass or lymphadenopathy
▪ Family history of upper gastrointestinal cancer
Perform upper endoscopy with gastric biopsy in all patients¶
Organic disease present
Upper endoscopy not performed
Organic disease absent
Organic disease absent
Organic disease present
Dyspepsia secondary to organic disease
Treat based on underlying diseaseΔ
Functional dyspepsia◊
Evaluate for active H. pylori infection on gastric biopsies
Dyspepsia secondary to organic disease
Treat based on underlying diseaseΔ
Biopsies not performed
H. pylori present
H. pylori absent
Test for H. pylori infection with stool antigen or urea breath test
H. pylori absent
H. pylori present
Treat for H. pylori and confirm eradication§
Persistent symptoms¥
Trial of proton pump inhibitor for 4 to 8 weeks
Persistent symptoms¥
Discontinue proton pump inhibitor‡
Trial of tricyclic antidepressant for 8 to 12 weeks
Persistent symptoms¥
Symptom improvement
Discontinue tricyclic antidepressant
Trial of prokinetic for 4 weeks
Continue for 6 months and then discontinue
Resume if symptoms recur
Persistent symptoms¥
Symptom improvement
▪ Re-evaluate symptoms
▪ Perform an upper endoscopy if not previously performed
▪ Assess gastric emptying in patients with nausea and vomiting predominant symptoms
▪ Trial of psychotherapy in patients with functional dyspepsia
Discontinue prokinetic and repeat 4 week course if symptoms recur

Algorism; approach to a patient with dyspepsia

* Gastric mucosal biopsies should be obtained at the time of upper gastrointestinal endoscopy to rule out infection with *H. pylori*.

¶ Additional evaluation may be required based on symptoms (eg, abdominal imaging in patients with concurrent jaundice or pain suggestive of a biliary/pancreatic source).

Δ Refer to UpToDate topic reviews.

◊ Patients with continued symptoms of dyspepsia for three months with symptom onset at least six months before diagnosis and no evidence of structural disease to explain the symptoms should be diagnosed and treated as functional dyspepsia.

§ Eradication of *H. pylori* infection can be confirmed with a urea breath test, stool antigen testing, or upper endoscopy-based testing performed 4 weeks after completion of antibiotic therapy. The choice of test depends on the need for an upper endoscopy (eg, follow-up of bleeding peptic ulcer) and local availability. *H. pylori* serology should not be used to confirm eradication of *H. pylori*. Refer to UpToDate topic on diagnostic tests for *H. pylori*.

¥ Allow 8 to 12 weeks before reassessing symptomatic response.

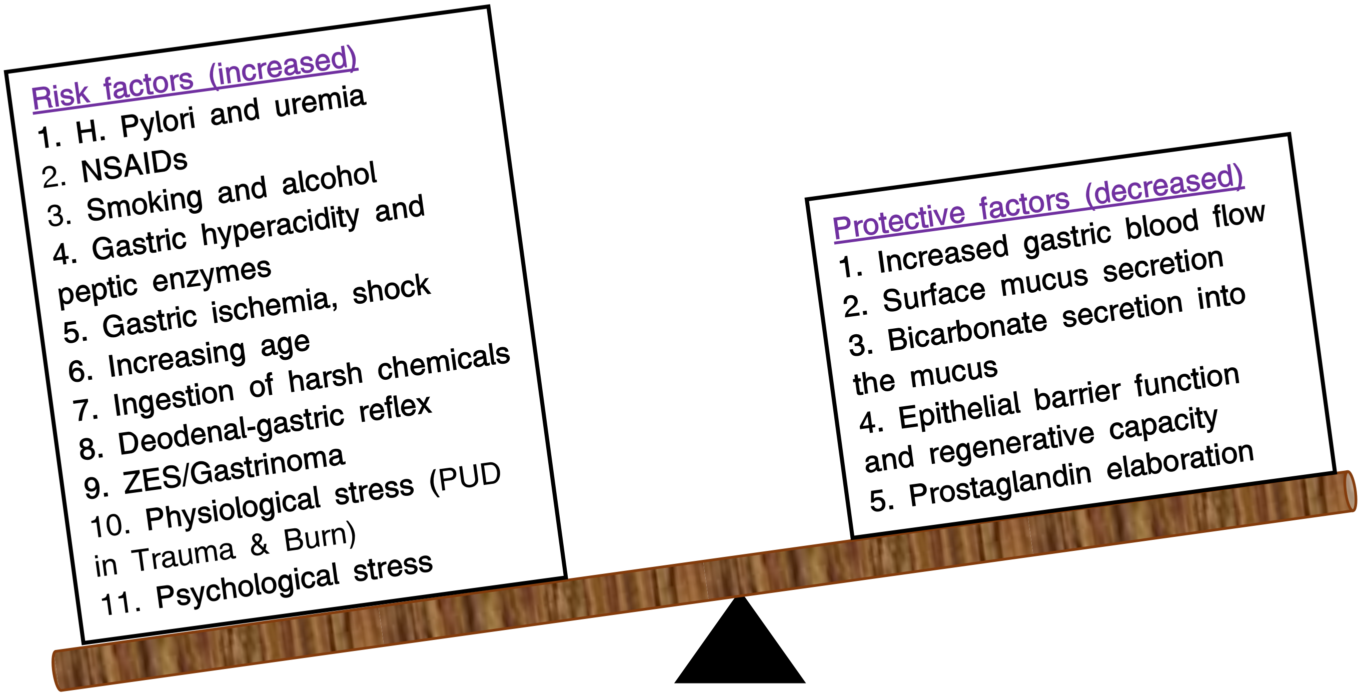
‡ For patients with a partial clinical response to a proton pump inhibitor, a tricyclic antidepressant can be initiated as combination therapy with a proton pump inhibitor.

3.8.3.2 Peptic ulcer disease (PUD)/የጨጓራ ቁስለት/

- Peptic ulcers are focal defects in the gastric or duodenal mucosa that extend into the submucosa or deeper.
- The natural history of PUD ranges from resolution without intervention to the development of **complications** like **bleeding, perforation & GOO (Gastric outlet obstruction).**
- **N.B anterior duodenal ulcer perforates and posterior duodenal ulcer bleeds. Perforation is more common in males (M:F ratio = 8-10:1)**
- **PUD needs both medical and surgical evaluation**

Pathophysiology

- PUD occurs due to imbalance between offending factors/risk factors/ and mucosal defense mechanisms. Any factor and stimuli that can compromise the protective mechanisms and/or intensify the damaging forces can result in mucosal injury and inflammation



Risk factors (increased)
1. H. Pylori and uremia
2. NSAIDs
3. Smoking and alcohol
4. Gastric hyperacidity and peptic enzymes
5. Gastric ischemia, shock
6. Increasing age
7. Ingestion of harsh chemicals
8. Deodenal-gastric reflex
9. ZES/Gastrinoma
10. Physiological stress (PUD in Trauma & Burn)
11. Psychological stress

Protective factors (decreased)
1. Increased gastric blood flow
2. Surface mucus secretion
3. Bicarbonate secretion into the mucus
4. Epithelial barrier function and regenerative capacity
5. Prostaglandin elaboration

Clinical features

- **Burning epigastric pain** (> 90%)
  - ✓ Patients with **duodenal ulcer** often experience **pain 2 to 3 hours after a meal** and **at night,** in which 2/3rd of patients with duodenal ulcers will complain of pain that awakens them from sleep.
  - ✓ The pain of **gastric ulcer** more commonly occurs **during eating .**
- **Associated symptoms**
  - ✓ Nausea, bloating

- ✓ Hematemesis/Melena

Investigations

1. **H.pylori tests (Stool antigen, Serum antibody)**
2. Upper GI endoscopy has both diagnostic & therapeutic importance → to look for ulcers, protruding mass or any active bleeding. Gastric mucosal biopsies should be obtained at the time of endoscopy to rule out infection with *H. pylori*.
3. **Barium meal** → It demonstrates barium within the ulcer crater.
4. **ECG**
    - ☛ ECG should be done **in elderly** patients & **patients with co-morbid illness** like DM, Hypertension & dyslipidemia who present with dyspeptic symptoms.
    - ☛ This will help you **to rule out** the life-threatening condition, **acute coronary syndrome**.
    - ☛ The rationale behind this workup is the consideration of the dyspepsia symptom in such patients could be an angina equivalent.
5. **Serum gastrin level**

Management of PUD

- ✓ Medical management is the same as Dyspepsia which is discussed above
- ✓ **Surgical treatment for PUD is indicated for:**
    - ▪ Perforation
    - ▪ Hemorrhage
    - ▪ Obstruction
    - ▪ Intractable ulcer

3.8.3.3 Gastroesophageal reflux disease (GERD)

- ✚ Some degree of brief reflux occurs physiologically; usually after a meal or during sleep.
- ✚ Gastro oesophageal reflux disease (GERD) refers to return of stomach contents in to the esophagus which is a pathologic reflux associated with symptoms and complications.
- ✚ GERD is a common in primary care practice. Due to its symptoms it can also be misdiagnosed.
- ✚ Based on the endoscopic appearance GERD is classified in to two types: **Erosive and non-erosive.**
    - ✓ Erosive GERD (Erosive esophagitis) is diagnosed when there are endoscopically visible breaks in the esophageal mucosa while non-erosive GERD shows no visible mucosal injury on endoscopy.
- ✚ GERD is associated with significant esophageal or extraesophageal complications.
    - o Esophageal complications

        - ♥ Barrett's esophagus: a precancerous change in the esophageal mucosa (from squamous epithelium to columnar epithelium)
        - ♥ Esophageal stricture: which manifests with solid food dysphagia and intermittent food impaction.
    - Extraesophageal complications
        - ♥ Triggering Asthma
        - ♥ Laryngeal and pharyngeal reflux: which manifests with chronic cough, repetitive throat cleaning, hoarseness of voice

Clinical manifestations

Symptoms

- The two major symptoms of GERD which are considered classic (typical) are **heartburn and regurgitation.**
    - Heartburn is a commonly described by patients as a burning sensation behind the sternum (retrosternal area).
    - Regurgitation is defined as back flow of gastric contests in to the mouth or pharynx. Patients feel an acidic (sour) content coming to the mouth mixed with small amounts of undigested food.

- Other symptoms
    - Chest pain: GERD associated chest pain can mimic angina
    - Triggering asthma attacks (wheezing)
    - Hoarsens of voice
    - Persistent cough
    - Nausea
    - Sensation of a lump in the throat (Globus sensation)
    - Increased salivation (Water brash)

Diagnosis and investigations

Diagnosis

- In patients with typical symptoms (i.e. heartburn or regurgitation), the diagnosis of GERD can be considered on clinical grounds without additional investigations, if there are no alarm signs. In such cases empiric therapy should be started.

Investigations

- Upper GI (gastrointestinal) endoscopy

- Endoscopy is not necessary to make a diagnosis of GERD but it is indicated in patients with alarm features to see evaluate for possible malignancy.
- The alarm features are
    - weight loss
    - age above 60 years
    - iron deficiency anemia
    - dysphagia
    - persistent vomiting
    - family history of cancer in parents or siblings.
- If GERD symptoms have been there for more than 5-10 years, endoscopy can be considered to look for evidence of Barrett's esophagus.

Treatment

Non-pharmacologic treatment

1. **Life style modifications → look at above**
2. Surgery
    - Surgical intervention (usually fundoplication) in GERD patients is **rarely indicated** in the following circumstances:
        - Large **hiatal hernia** causing the reflux symptoms
        - Evidence of **aspiration**
        - **Esophagitis refractory to medical therapy**
        - Persistent symptoms documented as being caused by **refractory GERD**: after checking compliance to PPI and optimizing PPI use.

Pharmacologic treatment

First line:

- **PPIs** → No major difference in between the available PPIs
    - Omeprazole 40mg PO daily for 8 -12 weeks OR
    - Esomeprazole 40mg PO daily for 8-12 weeks OR
    - Pantoprazole 40mg PO daily for 8-12 weeks
- Stop therapy on symptom resolution to assess response
- After the first 8 -12 weeks, resume therapy as needed → Intermittent OR On demand

Alternatives:

- **H2 blockers** → If PPIs are not available and the symptoms are mild

- Cimetidine 400mg BID for 8 weeks OR
- Ranitidine 150mg BID for 8 weeks OR
- Famotidine 20mg BID for 8 weeks

3.8.4 GI bleeding

- Gastrointestinal (GI) Bleeding refers to any bleeding that occurs from the mouth to the anus.
- Anatomically GI bleeding is divided in to upper and lower.
- The ligament of Treitz is used as the anatomic reference to differentiate lower and upper GI bleeding.

3.8.4.1 Upper GI bleeding

- Upper GI bleeding refers to gastrointestinal blood loss originating from the GIT is **proximal to the ligament of Treitz** at the duodenojejunal junction.
- It can be overt or occult bleeding.

1. **Overt** upper GI bleeding can manifest in the following ways:
    - **Hematemesis**: vomiting of frank red blood or a “coffee-grounds” material.
    - **Melena**: Passage of black, tarry stool
    - **Hematochezia**: passage of bright red or maroon (dark red) blood from the rectum. Upper GI bleeding causes hematochezia **rarely**, when it is massive and very acute.
2. **Occult** upper GI bleeding present **with symptoms anemia** such as lightheadedness, or a **positive fecal occult blood test** on routine testing.

Causes of Upper GI bleeding

- The two major causes that should be considered in every patient with overt upper GI bleeding are peptic ulcer disease and esophageal varices.

1. **Peptic ulcer disease**
2. **Esophageal varices**
3. Gastroduodenal erosions
4. Mallory-Weiss tears (esophageal mucosal tear due to vomiting or retching)

5. Esophagitis
6. Vascular malformations,
7. Neoplasm
8. Coagulopathy
9. Obscure upper GI bleeding: often from small intestinal lesions

Clinical features

Symptoms

- Nausea
- Vomiting of bright red blood or coffee-ground matter
- Melena
- Hematochezia: rare in upper GI bleeding but can occur in massive acute bleeding.
- Symptoms related to the underlying cause
    - ✓ Medication history: antiplatelet (aspirin, clopidogrel), NSAID or anticoagulants
    - ✓ Symptoms of portal hypertension or liver cirrhosis in patients with variceal bleeding e.g. ascites, fatigue.
    - ✓ The bleeding in varices is generally bright red, painless, brisk, and voluminous.
    - ✓ Long standing epigastric pain: Suggestive of PUD
    - ✓ Preceding forceful vomiting or retching suggests Mallory-Weiss tears
    - ✓ Weight loss: may indicate neoplasm

Signs

- Signs suggesting the hemodynamic status of the patient and the degree of anemia
    - ✓ Orthostatic hypotension
    - ✓ Resting tachycardia
    - ✓ Degree of pallor
    - Signs of the underlying cause of the upper GI bleeding
        - ✓ Signs of CLD or portal hypertension indicating the possibility of bleeding varices: Ascites, splenomegaly, encephalopathy.
        - ✓ Other site bleeding: platelet related disorders or coagulopathies

Diagnosis and investigations

Diagnosis

- The diagnosis is **clinical**→ a history of hematemesis or melena

- The next step in the diagnosis is trying to establish the cause of the upper GI bleeding.
- Upper GI endoscopy → has both diagnostic and therapeutic value.

Investigations

- CBC
- Serial hemoglobin/hematocrit every 8 hour→ the initial hemoglobin/hematocrit may be normal as the loss is whole blood (both plasma and cells)
- Coagulation profile: PT (INR) and PPTT
- Urea and Creatinine
- Liver enzymes
- Upper GI endoscopy

Risk stratification

- There are a few risk stratification tools which are useful to assess the likelihood of a person with upper GI bleeding to need further interventions like endoscopic treatment and transfusion.
- The Glasgow-Blatchford bleeding score (GBS) is one of the scores. It is simple risk stratification tool which does not require endoscopy. We recommend using the score

Table.: Glasgow-Blatchford bleeding score (GBS)

Risk marker		Value	Score
Urea (blood urea) (mg/dl)		38 - 46	2
		47 - 57	3
		58 - 146	4
		≥147	6
Hemoglobin (g/dl)	males	12 - 13	1
		10 - 12	3
		< 10	6
	females	10 - 12	1
		< 10	6
Systolic BP (mmHg)		100 - 109	1
		99 - 90	2
		< 90	3
Pulse ≥100 (per min)			1
Presentation with melena			1
Presentation with syncope			2
Hepatic disease			2

Heart failure	2
Interpretation of the score ✓ 0 → low risk ✓ 1-7 → high risk, keep in hospital as the patient is likely to require transfusion or endoscopic intervention ✓ ≥ 8 → requires ICU admission	

Treatment

1. Hemodynamic stabilization

- Monitor **airway, BP and PR.**
- Keep **NPO**
- Secure **double IV line** (considering transfusion and fluid mgt)
- **Treat hypotension** initially with rapid, bolus infusions of isotonic crystalloid
- Provide **transfusion** if either of the following is present
  - ✓ Hemodynamic instability (hypotension) is present.
  - ✓ Hemoglobin <9 mg/dL in high-risk patients (e.g. elderly, coronary artery disease)
  - ✓ Hemoglobin <7 mg/dL in low-risk patients

2. IV PPI for all patients

- ✓ Omeprazole 80mg IV loading followed by 40mg IV BID OR
- ✓ Esomeprazole 40 mg IV BID OR
- ✓ Pantoprazole 40 mg IV BID

3. Arresting bleeding

- **Endoscopic therapy** is the main stay of therapy to arrest bleeding After hemodynamic stabilization.
- **Balloon tamponade** may be performed as a temporizing measure for patients with uncontrollable hemorrhage after tracheal intubation.

4. Open surgery

- Indications for surgery
  - ✓ Hemodynamic instability despite vigorous resuscitation (> 3 units three of transfusion)
  - ✓ Shock associated with recurrent hemorrhage
  - ✓ Perforated PUD along with bleeding

- ✓ Failed endoscopic therapy for bleeding PUD
- ✓ No access to endoscopy therapy with ongoing bleeding
- ✓ Relative indications: difficult crossmatch, refusal of transfusion, shock on presentation,

5. **Treating the underlying cause**

- Patients with H. Pylori associated ulcer bleeding should receive eradication therapy.
- In NSAID or Aspirin associated bleeding ulcers: stop the drug and re-evaluate the need.
- Anticoagulants: stop and re-evaluate for continued need, dose adjustment if continued
- Variceal bleeding: band ligation and non-selective beta-blocker therapy (propranolol)
- Idiopathic (non-H. pylori, non-NSAID) ulcers: long-term PPI is recommended

3.8.4.2 Lower GI bleeding

- The incidence of lower GI bleeding is higher in older age groups, particularly in those taking anti-platelet agents like aspirin, NSAID's or anticoagulants.
- Lower GI bleeding can be overt or occult.
  - **Overt** lower GI bleeding presents with either frank red bleeding (**hematochezia**) or dark, tarry stool (**melena**).
  - **Occult** GI bleeding presents with evidence **of iron deficiency anemia** but no hematochezia or melena.
- Lower GI bleeding is labeled to be massive when it is associated with hemodynamic instability.

Causes of lower GI bleeding

1. Vascular causes
   - **Hemorrhoids**
   - Ischemic bowel
   - Vascular dysplasia (angiodysplasia)
   - Post procedure (post polypectomy)
2. Neoplastic causes
   - **Colon cancer**
   - Polyps

3. Anatomic causes
    - ✓ Diverticulosis
4. Inflammatory causes
    - ✓ IBD
    - ✓ Infectious colitis

Clinical manifestations

Symptoms

- ♥ **Hematochezia:** passage of bright red or dark red (maroon) blood or clots per rectum.
    - ✓ Bleeding from the **left colon tends to be bright red** in color while bleeding from the **right colon appears to be dark** or maroon colored and may be mixed with stool.
    - ✓ Bleeding from the right colon might rarely cause melena (the stool itself is dark)
- ♥ **Symptoms of anemia or hemodynamic compromise**: fatigue, postural dizziness, light headedness

Signs

- ♥ Signs of hemodynamic compromise:
    - ✓ Hypotension (supine or postural)
    - ✓ Resting tachycardia.
- ♥ Signs of anemia
    - ✓ Pallor
    - ✓ Tachycardia
    - ✓ Ejection systolic murmur

Diagnosis and investigations

Diagnosis

1. Identifying whether the bleeding is upper or lower GI in origin.

- ✓ **Massive upper GI bleeding can cause hematochezia**; hence, differentiating Upper from lower GI bleeding is necessary.
- ✓ The presence of **hemodynamic instability favors upper GI** bleeding
- ✓ The presence of **clots suggests lower GI** bleeding
- ✓ When there is suspicion of **upper GI source**: insert NG tube and do **gastric lavage** with normal saline
    - ♥ Gastric lavage with **coffee-ground material or bright red** blood= **upper** GI bleeding
    - ♥ Gastric lavage is **bilious = lower GI** bleeding

- ♥ If the gastric lavage is **neither of the above = indeterminate** (it can be either of the two)

2. Identifying possible causes or precipitants of the bleeding.

- ✓ The history should focus on the following

  - ➢ Medications: Antiplatelets (e.g. Aspirin or clopidogrel), NSAID's (e.g. Diclofenac, indomethacin, ibuprofen), anticoagulants
  - ➢ Prior history of bleeding
  - ➢ Significant abdominal pain: suggests inflammatory or ischemic bowel disease or perforation
  - ➢ Significant weight loss: suggests malignancy

- ✓ DRE

3. Localization of the bleeding and definitive diagnosis

- ✓ All patients with a clinical diagnosis of lower GI bleeding require **colonoscopic examination** to identify the cause of bleeding, arrest the bleeding if identifiable.

Investigations

- ☬ Baseline IX
  - ✓ CBC: in massive acute bleeding the hemoglobin may appear normal.
  - ✓ Serial hemoglobin; every 8 hours
  - ✓ Coagulation studies: INR (PT) and PTT
  - ✓ Liver enzymes
  - ✓ BUN and creatinine
- ☬ Colonoscopy: when the clinical diagnosis is lower GI bleeding
- ☬ Upper GI endoscopy: when the clinical diagnosis is upper GI bleeding.

Treatment

1. **Hemodynamic status evaluation and resuscitation**
   - o In patients with hemodynamic compromise secure two wide bore IV cannula and **resuscitate** with crystalloids.
   - o While crystalloids are being given, blood should be requested for **transfusion.**
     - ✓ Do not depend on the initial hemoglobin or hematocrit to for transfusion, as it is apparently ("falsely") normal.
2. **Discontinue antiplatelets, NSAID's or anticoagulants**
3. **Correct coagulopathies**

  - E.g. If INR is high or patients has been on warfarin, give fresh frozen plasma and/or vitamin K

4. **Surgical consultation**
   - In patients who continue to bleed massively and who are unstable to do colonoscopy or if colorectal cancer is suspected

3.9 UTI (የሽንት ቧንቧ ልክፍት/ኢንፌክሽን/)

- UTI (urinary tract infection) refers to the presence of microorganisms in higher numbers to cause invasion of the urinary tract (UT) epithelium and inflammation that cannot be accounted for contamination.

Classification of UTI

- UTI is classified in different ways that have implication to treatment and outcome

1. **According to anatomic site of involvement:**
   - ✓ **Lower UTI**: cystitis, urethritis, prostatitis
   - ✓ **Upper UTI**: pyelonephritis, involving the kidney

2. **According to the presence of structural urinary tract problems**
   - ✓ **Uncomplicated UTI**:
     - ☛ occurs in individuals who lack structural or functional abnormalities in the UT that interfere with the normal flow of urine.
     - ☛ Mostly in healthy females of childbearing age.
   - ✓ **Complicated UTI**:
     - ☛ occurs in individuals with structural or functional abnormalities in the UT that can interfere with normal flow of urine such as
       - congenital distortion of the UT
       - a stone
       - an indwelling catheter or the use of intermittent bladder catheterization
       - vesicoureteral reflux or other functional abnormalities
       - BPH
       - Obstruction
       - neurological deficit.
     - ☛ UTI in men and pregnant women can be classified as complicated.
     - ☛ RF risks for serious infections
       - Recent urinary tract instrumentation

  - peri-and postoperative UTI
  - CKD and transplantation
  - poorly controlled diabetes mellitus
  - immunosuppression (such as neutropenia or advanced HIV infection).
- In addition, patients should also be carefully evaluated for high risk of resistant infections

Recurrent UTI

- Multiple symptomatic UTIs with asymptomatic periods in between.
- Significant when there are ≥ 2 symptomatic episodes per year or it interferes with patient's quality of life.
- It is usually a reinfection than a relapse.
  - **Relapse:** Infection with same organism within 14 days of stopping antibiotics for previous UTI
  - **Reinfection:** a completely different organism; most common cause of recurrent cystitis

Bacteriuria

- **Asymptomatic bacteriuria**:
  - ✓ Bacteriuria > 10^5 bacteria/ml of urine without symptoms.
  - ✓ It is very common in elderly women and men.
  - ✓ Use of antibiotics for asymptomatic bacteriuria can drive antibiotic resistance and increase the risk for subsequent symptomatic UTI.
  - ✓ Asymptomatic bacteriuria should be treated in pregnant women and in men undergoing urological procedures. The benefits of therapy in other groups were questionable.
- **Symptomatic abacteriuria**:
  - ✓ Symptoms of urinary frequency and dysuria in the absence of significant bacteriuria

Etiologies

- ➔ The vast majority of acute symptomatic infections occur in young women.
- ➔ *E. coli* cause approxmatley 80% of acute infections in patients without catheters, stone or other urologic abnormalities. On the other hand, organisms like *klebsiella*, *enterobacteria*, *proteus*, *serratia* and *psuedomonas* assume greater importance in complicated and nosocomial UTIS.

Clinical features

- The range of possible symptoms caused by UTI is extremely broad, from no symptoms to symptoms referable to the lower urinary tract (e.g. dysuria and frequency), to symptoms indicative of an upper UTI (e.g. loin pain, fever, chills and costo-vertebral angle tenderness), to full-blown urosepsis.

- **Lower UTI (Cystitis)**
  - Commonly dysuria, frequent urination and urgency; Occasionally, gross hematuria, Suprapubic pain
  - Elderly people may have nonspecific symptoms only (like chronic dysuria or urinary incontinence, mental status changes, abdominal pain and decreased eating or drinking)
  - Chronic nocturia or chronic incontinence, general malaise, and cloudy or malodorous urine are nonspecific features that should not routinely swift for cystitis evaluation and treatment.

- **Upper UTI (pyelonephritis)**
  - dysuria, frequent urination and urgency, hematuria
  - Systemic symptoms like fever, chills, rigors, and marked fatigue or malaise beyond baseline, nausea, vomiting
  - Suprapubic pain
  - Costovertebral angle tenderness; flank pain
  - Pelvic or perineal pain (in men),
  - Elevated WBC
  - Elderly people may have nonspecific symptoms only (like mental status changes, abdominal pain and decreased eating or drinking)

Investigations and diagnosis

Clinical

- signs and symptoms and urinalysis are the common diagnostic methods
- Digital rectal examination (DRE): For men with symptoms of pelvic or perineal pain, DRE might be warranted to evaluate a tender or edematous prostate, suggesting **acute prostatitis.**

Urine analysis

- pyuria (WBC > 10 cells/mm3)
    - present in almost all patients with UTI.
    - Hence, its absence suggests alternative diagnosis particularly in patients with nonspecific symptoms.
- bacteriuria → >10^2 CFU/ml is diagnostic.
    - Significant bacteriuria → presence of 10^5 CFU/ml of urine in clean catch specimen.
    - In women with symptomatic UTI a lower bacterial count should be used as 1/3 of symptomatic women have <10^5 CFU/ml. (e.g. 100 CFU/ml will have higher positive predictive value)
- Cloudiness
- Red blood cells
- Nitrite positive (E. coli, Proteus, Klebsiella),
- Leukocyte esterase positive,
- Casts (if pyelonephritis)
    - fever and flank pain, even in absence of typical symptoms of cystitis may suggestive for pyelonephritis.

Urine gram stain and culture

- Blood cultures → +ve in 20% of patients with upper UTI
- Indication for blood culture
    - complicated UTI
    - recurrent UTI
    - Pyelonephritis
    - urosepsis.

- **Imaging**:
    - e.g. Abdominal U/S (kidneys and urinary tract)- indicated in
        - complicated UTIs (suspected obstruction, severely ill)
        - poor responders and recurrent UTIs.
    - Radiology helps to see calculus or obstruction or abscess

Treatment

Non pharmacologic

- Postcoital voiding and liberal fluid intake for women with recurrent UTI
- Manage underling anatomical or functional urinary obstruction or

abnormality.

- ☛ Antimicrobials alone might not be effective unless correcting such underlying conditions.
- ☛ Patients with neurogenic bladder, indwelling bladder catheters, nephrostomy tubes, and urethral stents may require additional intervention, like more frequent catheterization to improve urinary flow, exchange or removal of a catheter, or urologic/gynecologic consultation.

Pharmacologic

A. Acute uncomplicated lower UTI (cystitis)

First line

- ✓ Ciprofloxacin 250- 500mg PO, BID for 3 days **or**
- ✓ Norfloxacin, 400mg PO., BID, for 3 days. **or**
- ✓ Cotrimoxazole (TMP-SMO) 960mg (160/800mg) P.O, BID for 3 days **or**
- ✓ Nitrofurantoin 50mg P.O., QID for 7 days (effective if available)

Alternative

- ✓ Fosfomycin 3g single dose OR
- ✓ Cefpodoxime100mg PO, BID for 5 days *OR*
- ✓ Amoxicillin-clavulanate 500/125mg TID for 5 days

B. Mild to moderate upper UTI

- ☛ like pyelonephritis, known comorbidities and with immunosuppression
- ☛ *able to take orally with no vomiting, no dehydration, no evidence of sepsis*

First line

- ✓ Ciprofloxacin, 500mg P.O., BID, oral for 7-10 days.

NB: for the following indications

- ✓ For patients requiring temporary emergency admission
- ✓ in a community with local flurorquinolone resistance >10% (may be true for certain settings in Ethiopia)
- ✓ patients intolerant to fluoroquinolone

use the following

- ✓ single dose ceftriaxone (1 gram IV or IM) initially or
- ✓ Ertapenem (if available) 1 gram IV or IM or
- ✓ gentamicin 5 mg per kg IV or IM, once)

- can be administered along with or followed by an oral fluoroquinolone (if no tolerance issue)
- Among the available fluoroquinolones, moxifloxacin attains lower urinary levels than others and should not be used for UTI

Alternative

- ✓ Cotrimoxazole, 960mg P.O, BID for 14 days. Or
- ✓ Cefpodoxime proxetil, 200mg P.O., BID for 10 days (β-Lactam for 10—14 days; less effective than first two options)

C. Severe acute upper UTI

- (e.g. pyelonephritis) *(high grade fever, vomiting, dehydration, or evidence of sepsis)* without risk of resistant infections → *start IV*

First line

- ✓ Ciprofloxacin, 400mg, I.V, BID or
- ✓ ceftriaxone, 2gm, I.V, daily or 1gm, I.V, BID
  till patient improves (usually at 48 - 72 hours) and then continue
- ✓ Ciprofloxacin 500mg, PO, BID to complete 10-14 days course, on discharge.

Alternative

- ✓ Ceftriaxone or cefotaxime co-prescribed with gentamycin/ amikacin

D. Severe acute UTI with risk of resistant infections

First line

- ✓ Meropenem 1gm IV TID **OR**
- ✓ Imipenem 500mg IV QID

Alternative

- ✓ ceftazidime 2 gm IV TID or
- ✓ cefepime 2 gm IV TID
- ✓ piperacillin-tazobactam 3.375 gm IV QID
  - ○ piperacillin-tazobactam may be used as an initial agent due to its advantage of covering gram positive cocci (staphylococci and enterococci) infections.

- Vancomycin may be added based on the potential for MRSA (e.g. previous MRSA isolate from the patient)

E. Recurrent UTI

- ✓ Antibiotic prophylaxis is recommended for
  - ▪ women who experience ≥ 2 symptomatic UTIs within 6 months or ≥ 3 over 12 months.
  - ▪ Recurrent pyelonephritis.
- ✓ Any prophylaxis should be given after current active infection is treated.
- ✓ Recurrent infections might be a relapse or reinfection
  - ❖ **Relapse**: assess pharmacologic reason for treatment failure. Use longer treatment courses (for 2 - 6 weeks, depending on

length of initial course)

- ❖ **Reinfection**: reassess need for continuous prophylactic antibiotics every 6 - 12 months.

1) If patient has ≤ 2 UTIs in 1 year, use therapy for symptomatic episodes only (3-day treatment regimens).
2) If patient has ≥ 3 UTIs in 1 year and they are temporally related to sexual activity
    - ☛ use post-intercourse prophylaxis with
        - cotrimoxazole single strength or
        - cephalexin 250 mg or
        - nitrofurantoin 50 - 100 mg and
    - ☛ counsel on voiding after intercourse. Postcoital voiding and liberal fluid intake is also recommended.
3) If patient has ≥ 3 UTIs in 1 year that are not related to sexual activity
    - ☛ use daily or 3X/week prophylaxis with
        - trimethoprim 100 mg or
        - cotrimoxazole single strength or
        - cephalexin 250 mg or
        - nitrofurantoin 50 - 100 mg.

- Usually duration of antibiotics is for six months followed by observation.
- If recurrent UTI comes again the prophylaxis can be prolonged for 1-2years.

F. Prostatitis

- considered in men presenting with cystitis symptoms that are recurrent or are accompanied by pelvic or perineal pain.
- Primarily caused by gram-negative organisms.

1. **Acute bacterial Prostatitis**:
    - Fluroquinolones or cotrimoxazole for 4 weeks is first line agents.
2. **Chronic bacterial prostatitis:**
    - Difficult to treat
    - similar antibiotics to acute bacterial Prostatitis are used but for a duration of 1 - 4 months.

G. Epididymitis

a. In patients older than 35 years
    - enteric organisms are the most probable causes.
    - Fluroquinolones or cotrimoxazole for 10 days to 4 weeks

b. In patients younger than 35 years
  - gonococcal or chlamydial infections are more probably causes.
  - ceftriaxone 250 mg IM once plus doxycycline 100 mg BID for 10 days.

Special population considerations

Pregnancy

- pregnant women should be screened for bacteriuria and treated, even if asymptomatic.
- Antibiotic options recommended for
  - ❖ uncomplicated UTI in pregnant women were:
    - ✓ Augmentin for 3-5 days
    - ✓ cephalexin or cefpodoxime for 3-5 days
    - ✓ Nitrofurantoin (avoid at term if other options available) for 5 days.
  - ❖ For sever or complicated scenarios
    - ✓ 3rd generation cephalosporin's (cefotaxime or ceftriaxone).
  - ❖ In the presence of a risk for resistant infections the following can be used as indicated for sever acute pyelonephritis.
    - ✓ piperacillin-tazobactam or
    - ✓ cefepime or
    - ✓ ceftazidime

  - ☛ Antibiotics to be avoided for pregnant are
    - ➔ Fluoroquinolones
    - ➔ aminoglycosides and
    - ➔ cotrimoxazole (used frequently but avoid especially during the late 3rd trimester).

Paediatrics

Lower uncomplicated UTI (acute cystitis)

- First line agents:
  - ✓ Cotrimoxazole, 48mg/kg/day, PO, BID for 3- 5 days *(available syrup preparation 240mg/5ml)*
    - o not recommended in the **first 6 weeks** of life.
- Alternatives
  - ✓ Augmentin 50-80mg/kg/day, PO, TID for 3-5 days *(available syrup preparation 400mg/5ml or 200mg/5ml)* or
  - ✓ Amoxicillin 50-80mg/kg/day, PO, TID for 3-5 days *(available syrup preparation 250mg/5ml, or 125mg/5ml)*

❖ **Fluoroquinolones are not recommended** in paediatrics unless for sever complicated conditions in the absence of other alternatives (if no alternative Ciprofloxacin 10 mg/kg/dose, BID or TID, for 3 days).

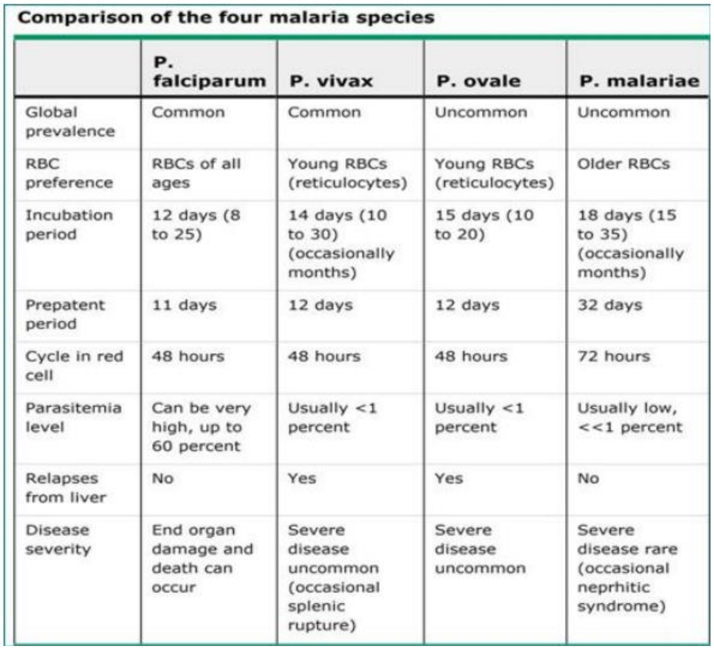
Upper uncomplicated UTI (Acute pyelonephritis)

- First line agents:
  - ✓ Ceftriaxone 50-80 mg/kg IV daily
  - ✓ Following initial response to parenteral therapy: Consider changing to: Cefixime 16 mg/kg the first day then 8 mg/kg/day, po, daily or BID to complete 10 days
- Alternatives
  - ✓ Ampicillin 50mg/kg/dose QID plus
  - ✓ Gentamycin 7.5mg/kg daily

3.10. Acute febrile illness (AFI)

3.10.1 Malaria (ወባ)

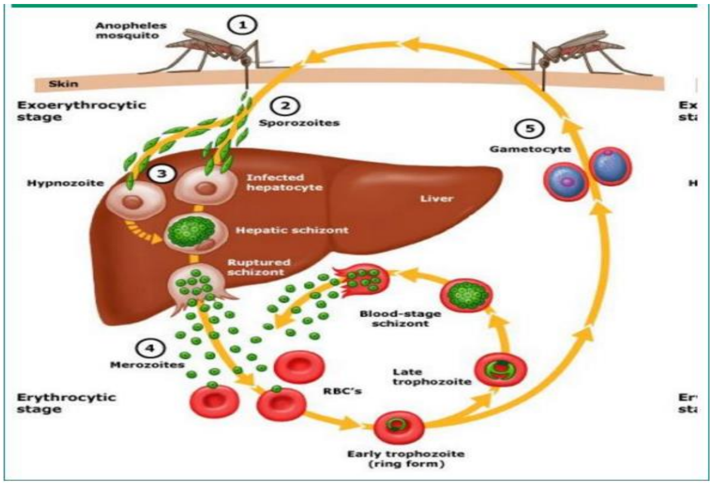
- ➢ Protozoan disease transmitted by the bite of infected female anopheles mosquito
- ➢ Aetiology: five Species of the genus plasmodia
  - — P. Falciparum
  - — P. Vivax
  - — P. Ovale
  - — P. Malariae
  - – P. Knowlesi
- **the commonest causes of Malaria in Ethiopia are P. Falciparum & P. vivax**



Comparison of the four malaria species

	P. falciparum	P. vivax	P. ovale	P. malariae
Global prevalence	Common	Common	Uncommon	Uncommon
RBC preference	RBCs of all ages	Young RBCs (reticulocytes)	Young RBCs (reticulocytes)	Older RBCs
Incubation period	12 days (8 to 25)	14 days (10 to 30) (occasionally months)	15 days (10 to 20)	18 days (15 to 35) (occasionally months)
Prepatent period	11 days	12 days	12 days	32 days
Cycle in red cell	48 hours	48 hours	48 hours	72 hours
Parasitemia level	Can be very high, up to 60 percent	Usually <1 percent	Usually <1 percent	Usually low, <<1 percent
Relapses from liver	No	Yes	Yes	No
Disease severity	End organ damage and death can occur	Severe disease uncommon (occasional splenic rupture)	Severe disease uncommon	Severe disease rare (occasional neprhitic syndrome)

Life cycle of plasmodia


Anopheles mosquito
①
Skin
Exoerythrocytic stage
②
Sporozoites
⑤
Gametocyte
Hypnozoite
③
Infected hepatocyte
Liver
Hepatic schizont
Ruptured schizont
Blood-stage schizont
④
Merozoites
Late trophozoite
RBC's
Erythrocytic stage
Early trophozoite (ring form)

1. Plasmodium-infected Anopheles mosquito bites a human and transmits sporozoites into the bloodstream.
2. Sporozoites migrate through the blood to the liver where they invade hepatocytes and divide to form
multinucleated schizonts (pre-erythrocytic stage).
3. Hypnozoites are a quiescent stage in the liver that exist only in the setting of P. vivax and P. ovale infection. This liver stage does not cause clinical symptoms, but with reactivation and release into the circulation, late onset or relapsed disease can occur up to many months after initial infection.
4. The schizonts rupture and release merozoites into the circulation where they invade red blood cells. Within red cells, merozoites mature from ring forms to trophozoites to multinucleated schizonts (erythrocytic stage).
5. Some merozoites differentiate into male or female gametocytes. These cells are ingested by the Anopheles
mosquito and mature in the midgut, where sporozoites develop and migrate to the salivary glands of the mosquito. The mosquito completes the cycle of transmission by biting another host.

Epidemiology

- Approximately 60% of the Ethiopian population live in malaria risk areas.
- Majority of malaria cases have been due to *P. falciparum*, with the remainder caused by *P. vivax*.
- Principal determinants of the epidemiology of malaria
  1. Number, Density, human — biting habit and longevity of the vector. Eg.
     Anopheles gambae is long-lived, breed readily, high density in the tropics,
     preferably bites humans to other animals
  2. Entomologic inoculation rate • Sporozoite + ve mosquitoes/Person /Yr (>300 in tropical Africa)

- Endemicity of malaria is determined by parasitaemic rates or palpable spleen
  rates in children 2-9 yrs of age
  - ✓ Hypo endemic - <10%
  - ✓ Meso endemic - 11-50%
  - ✓ Hyperendemic - 51-75%
  - ✓ Holoendemic - > 75%

Malaria Transmission pattern

1. Stable malaria transmission

- Transmission throughout the year
- Fairly uniform intensity of transmission with little variation over the years
- Long- living and frequently biting mosquitoes present
- High immunity in the community due to intense transmission
- Young children and pregnant women are susceptible groups
- Eradication of malaria is very difficult

2. Unstable Malaria transmission

- Uneven, erratic, less intense transmission
- Liable to flare-up into dramatic epidemics
- Short lived and less frequently biting mosquitoes present
- Low immunity status of the community
- All age groups are frequently affected
- Eradication of malaria is much easier than stable malaria

Pathogenesis

- The disease in humans is caused by the direct effects of RBC invasion and destruction by the asexual parasite and the host's reaction
- NB: Almost all deaths are caused by falciparum malaria

Pathogenesis of falciparum malaria

- ✓ RBC membrane changes result in cytoadherence and rosette formation → sequestration of red cells containing mature form of the parasite in vital organs (particularly the brain) → interfere with microcirculatory flow & metabolism
- ✓ Splenic immunologic and filtration clearance functions → accelerated removal of both parasitized and uninfected RBCs
- ✓ Both humoral and cell mediated immunity are necessary for protection. Immune individuals have a polyclonal increase in serum levels of IgM, IgG and IgA,
  although much of this antibody is unrelated to protection.

Host Factors: -

Geographic distribution of sickle cell disease, thalassemia and G6PD Deficiency closely resemble that of malaria before introduction of control measures

- Sickle cell disease - low O_2 tension - ↓parasite growth
  — ↓Severity of malaria (↓MR)

Factors retarding development of (cellular) immunity to malaria

- Absence of MHC-Ags on infected RBCs Surface
- Malaria Ag- Specific immune unresponsiveness
- Strain- Diversity of malarial parasites
- Expression of changing immunodominant Ags on RBC surface

Clinical features of Uncomplicated Malaria

Symptoms

- Lack of sense of wellbeing
- Headache, Fever, sweating
- Fatigue, Arthralgia, myalgia
- Abdominal pain, diarrhoea, Vomiting, anorexia
- NB - the classical malaria paroxysms of fever spikes, chills and rigors occurring at regular interval (relatively unusual) signify infection with P. vivax or P. ovale

Signs

- Fever, Tachycardia, Postural hypotension, Delirium
- Pallor, Hepatosplenomegaly, mild Jaundice

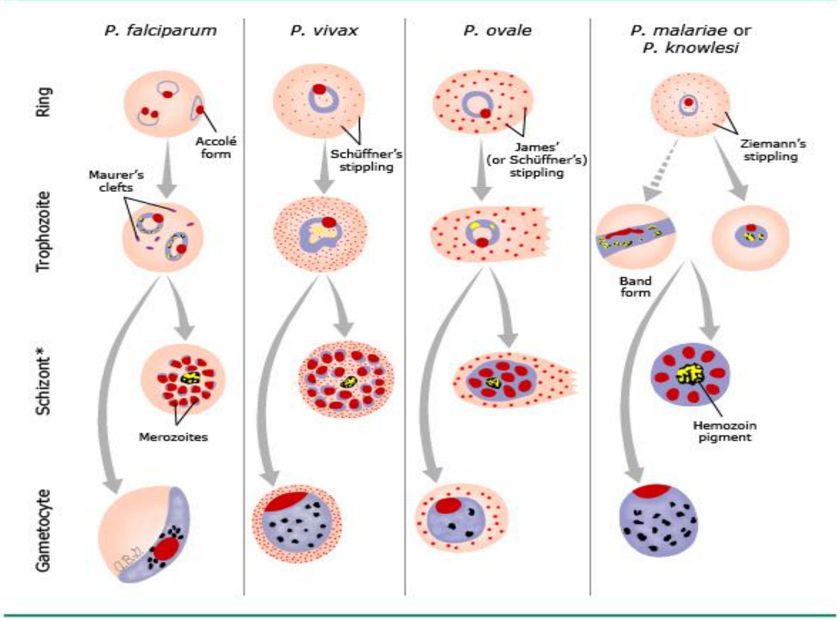
clinical diagnosis

- a patient from malaria endemic area has fever or history of fever in the last 48 hours or a patient from non-malaria endemic area has fever or history of fever in the last 48 hours and has a history of travel to malaria endemic areas within the last 30 days and spending at least one night.
- Making the diagnosis of malaria on clinical features alone is not recommended, as this often has low specificity and increases the chances of the patient being misdiagnosed.
- The health worker examining a suspected malaria case should look for other causes of fever (e.g. typhoid fever, relapsing fever, ARTI, meningitis, schistosomiasis, visceral leishmaniasis)

Laboratory diagnosis

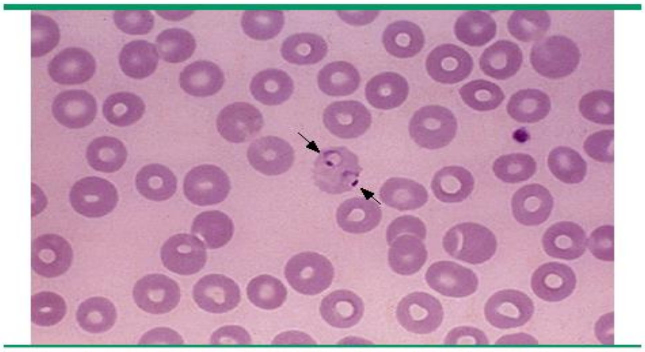
- Microscopy→ Demonstration of the parasite by peripheral blood smear
  - Thick and thin blood smear (100 - 200 thick field exam). Light microscopy using thick blood films can be very sensitive, detecting as few as 5 parasites/μl of blood.
  - Diagnosis of malaria
  - Species identification
  - Determination of parasitaemia (8000 wbc/μl assumption)

Red blood cell morphology in various forms of *Plasmodium* infections


P. falciparum
P. vivax
P. ovale
P. malariae or P. knowlesi
Ring
Trophozoite
Schizont*
Gametocyte
Accolé form
Maurer's clefts
Schüffner's stippling
James' (or Schüffner's) stippling
Ziemann's stippling
Band form
Merozoites
Hemozoin pigment

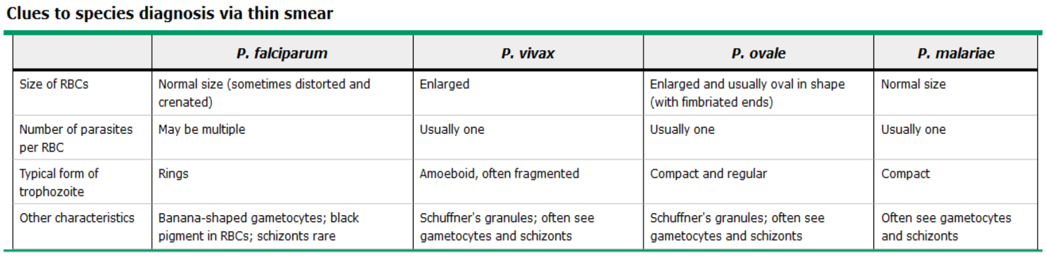
* Identification of a schizont with >12 merozoites in the peripheral circulation is an important diagnostic clue for *P. vivax*. In general, schizonts of *P. falciparum* are very rarely seen in blood films; they are generally absent from the peripheral circulation except in cases of severe infection with overwhelming parasitemia.

Malaria: Red cell containing intraerythrocytic ring forms (trophozoites)



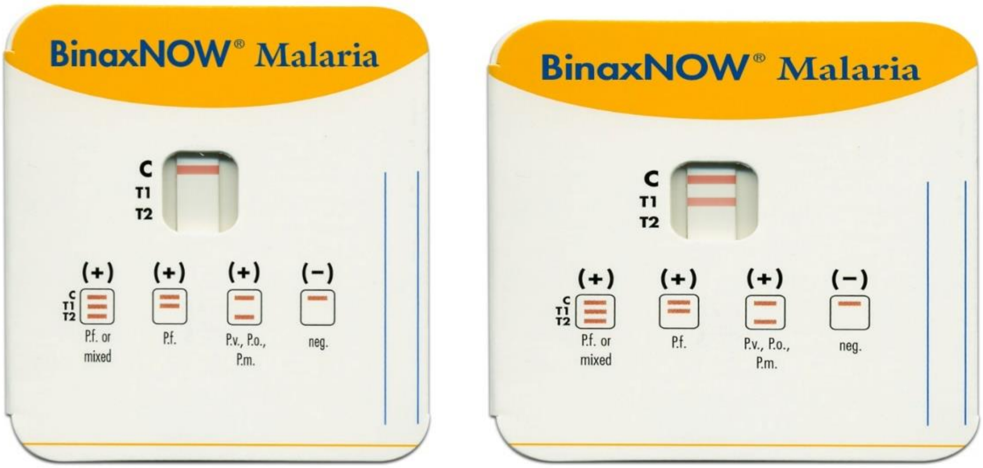
Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows).

Clues to species diagnosis via thin smear



	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*
Size of RBCs	Normal size (sometimes distorted and crenated)	Enlarged	Enlarged and usually oval in shape (with fimbriated ends)	Normal size
Number of parasites per RBC	May be multiple	Usually one	Usually one	Usually one
Typical form of trophozoite	Rings	Amoeboid, often fragmented	Compact and regular	Compact
Other characteristics	Banana-shaped gametocytes; black pigment in RBCs; schizonts rare	Schuffner's granules; often see gametocytes and schizonts	Schuffner's granules; often see gametocytes and schizonts	Often see gametocytes and schizonts

- Ab-based diagnostic stick /card test /RDT/ → if microscopy is unavailable
  - Detect P. falciparum specific histidine rich protein-2 (PfHRP-2) or lactate dehydrogenase antigen
  - Remain positive for weeks after infection



Immage; Rapid malaria test; T1 Positive → Positive result for *P. falciparum* (P.f.), T2 Positive → Positive result for *P. vivax* (P.v.) or *P. malariae* (P.m.) or *P. ovale* (P.o.) In some cases the appearance of only the T2 Line may indicate a mixed infection with two or more of P.v., P.m., and P.o., T1 + T2 Positive → Positive result for *P. falciparum* (P.f.) In some cases the appearance of both the T1 and T2 Lines may indicate a mixed infection of P.f. with another species, No T1 or T2 Lines → Negative result (no malaria antigens were detected)

For more about rapid malaria test, click here → Rapid malaria test

Treatment of uncomplicated Malaria

P. falciparum

- Coartem (Artemether (120mg) - Lumefantrine (20mg)) combined tablets 4 tabs po bid for 3 days.
- **AL and single dose primaquine** is the recommended first-line drug

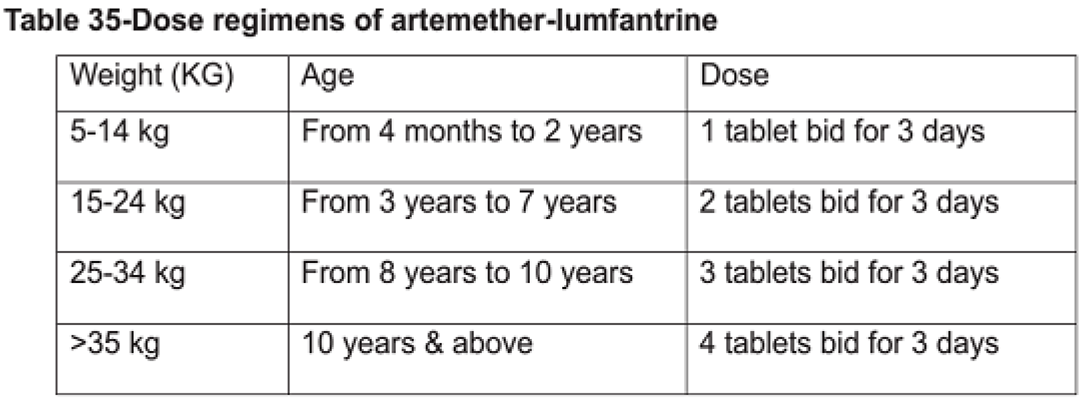


Table 35-Dose regimens of artemether-lumfantrine

Weight (KG)	Age	Dose
5-14 kg	From 4 months to 2 years	1 tablet bid for 3 days
15-24 kg	From 3 years to 7 years	2 tablets bid for 3 days
25-34 kg	From 8 years to 10 years	3 tablets bid for 3 days
>35 kg	10 years & above	4 tablets bid for 3 days

- **So, the usual dosage of coartem for adults is → Coartem,4 tabs, po, BID, for 3 days**
- **To reduce the transmission** of *P. falciparum* infection, give a **single dose of 0.25 mg/kg primaquine** with AL (except pregnant women, infants aged < 6 months and women breastfeeding infants aged <6 months. and testing for G6PD deficiency is not required during primaquine treatment

P. Vivax /P. Ovalle

- Chloroquine 150 mg base or chloroquine syrup 50 mg base;
  - ✓ **1g (4 tablets) at 0 and 24 hours. It is followed by 500mg (2 tablets) at 48 hrs.** 0r
  - ✓ 1 g (4 tablets) initially, then 500mg (2tablets) in 6 hours, it is then followed by 500mg (2ablets), PO, daily for 2 days. or
  - ✓ 10 mg base/kg/day, PO, TID, 1st and 2nd days, and 5mg base/kg/day, PO, TID, on 3rd day for 3 days (for a total dose of 25 mg chloroquine base/kg with a maximum total of 1,500 mg

chloroquine base /= maximum of 2,500 mg chloroquine phosphate salt/).

- ✓ A tablet of 250 mg chloroquine phosphate ("salt") is the same as chloroquine 150 mg base.

PLUS

- **primaquine 15mg po/d (0.25mg/kg /day) for 14 days** for hepatic hypnozoite clearance.

❖ N.B. Coartem (AL) may be used to treat P. vivax infection when chloroquine is not available.

P. *falciparum* and P. *vivax* (mixed infection):

- The recommended first line treatment for mixed infection is Coartem (AL) and single dose primaquine
- Alternative; quinine for 7 days + Primaquine for 14 days

Alternative treatment for uncomplicated malaria:

- AL for 03 days and primaquine for 14 days may be used to treat *P. vivax* infection when chloroquine is not available.
- If AL is not available for *P. falciparum* or mixed malaria infections, use oral quinine with single dose premaquine.
    - ✓ **10 mg/kg quinine sulphate salt** (= 8.3 mg base/kg)**, TID, for 7 days.** (The maximum adult dose is **600mg quinine sulphate (salt), PO, TID, for 7 days.)**
- If both chloroquine and AL are not available for *P. vivax* infection, use oral quinine.

Supportive treatment:

- If patients, especially children present fever of ≥37.5° C, treat with antipyretics and, if necessary, fanning and tepid sponging.
    - ✓ Paracetamol (acetaminophen) 15 mg/kg every 4 hours is widely used; it is safe and well tolerated, given orally or as a suppository

N.B

- Though the prevalence of G6PD deficiency is very low in Ethiopia, **closely follow**-up patients started on **primaquine for haemolysis** by directly observing the treatment, doing serial haemoglobin test and checking for darkening of urine. If there is evidence of haemolysis, primaquine should be discontinued and should not be given to the patient in the future.

Severe Falciparum Malaria

Manifestations (Danger signs) of severe malaria

In the presence of positive BF for asexual form P. falciparum

Clinical features

- Unarousable coma/cerebral malaria
- Respiratory distress (acidotic breathing/deep breathing or in-drawing of chest wall) → acidaemia/acidosis
- Severe anaemia (normochromic, normocytic) → paleness of palms is most reliable symptom in children
- Renal failure
- Pulmonary oedema/ ARDS
- Hypoglycaemia
- Hypotension/shock
- Bleeding/DIC
- Convulsions or recent history of convulsions
- Haemoglobinuria (cola coloured urine)
- Other
  - Impaired consciousness/arousable
  - prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance.
  - Unable to eat or drink
  - Repeated vomiting, resulting in inability to retain oral medication
  - Severe dehydration
  - Jaundice (yellowish discoloration of the eyes)
  - No urine output in the last 24 hours

Laboratory findings

- Severe anemia (hemoglobin <5g/dl, haemocrit < 15%)
- Hypoglycemia (< 40 mg/dL)
- Acidosis (bicarbonate <15 mmol/L)
- Hyperlactatemia (>5 mmol/L)
- Hyperparasitemia (>4% parasite density or >200,000 parasites per ul of blood in non-immune person)
- Renal impairment (creatinine >3mg/dl)

Essential laboratory tests for severe malaria

- The diagnosis of severe malaria is based on clinical features and confirmed with laboratory testing. While confirmation of the diagnosis is necessary treatment must be started promptly and not withheld while confirming the diagnosis
- Parasitological test (microscopy), If not use RDT
- RBS
- CBC, if not HgB and HCT
- Blood grouping and cross-matching
- BUN and creatinine
- Lumbar puncture to exclude meningitis or cover with appropriate antibiotics.

Differential diagnosis of severe malaria

Decreased Level of Consciousness

- Viral encephalitis
- Bacterial meningoencephalitis
- Cerebral typhoid
- Cerebro-vascular event (stroke)
- Complicated typhus, relapsing fever
- Febrile illness with hypoglycaemia
- Sepsis
- Convulsion in a patient with fever

Renal failure

- Glomerulonephritis (AGN)
- Acute tubular necrosis (ATN) due to hypovolemia or hypotension

Jaundice associated with fever

- Viral hepatitis
- Yellow fever
- Acute cholecystitis
- Choledocholithiasis

Treatment of severe malaria

If clinical features strongly suggest severe *P. falciparum* malaria, treatment maybe started even though results are negative (**Note:** This should be a **VERY** rare circumstance).

- Admit the patient

- Position semi-prone or on side
- Make rapid clinical assessment and Maintain ABC of life
- Exclude or treat hypoglycemia (more so in pregnant women)
- Insert NG tube for feeding and medication and urinary catheter/glove catheter for UOP determination
- Ensure nutrition and nursing care
- Take blood while establishing an IV line for IX
- If fever exceeds 39°C, remove patient's clothes, use tepid sponge,
- Consider other infections and broad spectrum antibiotics.
- Consider need for anti-convulsant treatment

Pharmacologic mgt

Treatment for severe malaria is either:

First line

- Artesunate, IV or IM

Alternative

- Artemether, IM

If artesunate or artemether are not available

- Quinine infusion, IV or
- Quinine, IM

- **Artesunate** 2.4 mg/kg (for Children weighing < 20 kg, 3 mg/kg/dose) IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day for 5 days or until the patient tolerates PO medication. If the patient tolerates after 24 h, the medication can be changed to PO AL for the next 3 days. If AL is contraindicated, continue treatment with quinine tablets.
- If Artesunate not available, give **quinine Infusion**
    - ✓ **Start IV quinine 20mg/kg in 500ml D5 or NS to run over 4 hrs loading then Maintenance dose should be given 12 hours after the start of the loading dose at a dose of 10 mg/Kg in 500ml D5 or NS to run over 4hrs, TID, for at least 48hrs**
    - ✓ ↓ dosage by 1/3rd to half, if required to treat with IV quinine after 48 hours (6 doses including the loading dose). It is unusual to continue IV infusions of quinine for more than 4-5 days;
    - ✓ Rapid administration of quinine is not safe and may cause sudden death due to arrhythmia or refractory hypotension. The infusion rate should not exceed 5 mg salt/kg/hr
    - ✓ If for any reason quinine cannot be administered by IV infusion, quinine dihydrochloride can be given in the same dosages by IM injection in the anterior thigh (not in the buttock). The dose of

quinine should be divided between two sites — half the dose in each anterior thigh. If possible, for IM use, quinine should be diluted in normal saline to a concentration of 60 - 100mg salt/ml;

- ✓ A loading dose of quinine should not be used if (i) the patient received quinine within the preceding 24 hours; (ii) mefloquine within the preceding 24 hours; or (iii) mefloquine within the preceding seven days;
- ✓ Quinine is not given by subcutaneous injection;
- ✓ Quinine is safe in pregnancy and in anaemic patients, if the doses are carefully calculated by body weight.
- ✓ **The parenteral treatment should be changed to P.O. only after 24 hours and as soon as the patient's condition improves and if there is no vomiting.**
- ✓ **Oral treatment should be given with *Artemether + Lumefantrine*. However, if a patient has a history of intake of *Artemether + Lumefantrine* before complications developed, give Quinine tablets 10 mg salt/kg TID to complete 7 days treatment.**

- ❖ Re-check malaria blood smear by microscopy after 48 hours to assess effects of anti-malarial treatment on blood parasite density;

1.1 Cerebral Malaria

- In repeated malarial attack if the last attack is ≥ 10 years, no risk of cerebral malaria (i.e. for cerebral malaria, the last attack should be < 10 years)

Clinical features

- Have nuchal rigidity, fever and headache
- Cmn in endemic area
- LOC for > 30 minutes
    - ✓ Repeated seizure without gaining consciousness
    - ✓ Cerebral malaria is unlikely in fully awake patients

Management

- Ensure ABC of life, coma care, feeding, bladder and bowel care, detection and treatment of other complications like aspiration
- Start artesunate immediately
- Broad spectrum antibiotic to cover other DDX like meningitis (if possible do LP before initiating antibiotic)

1.2 Hypoglycemia

- Give 50% dextrose (0.5gm/Kg) followed by infusion of 10% dextrose (0.1 gm/kg/hr)

- Correct hypoglycaemia (< 40 mg/dl) if present by infusing dextrose over a period of 3-5 minutes. This can consist of any one of the following:
    - ✓ 1 ml/kg of 50% dextrose diluted with an equal volume of NS (1ml/kg) IV slowly over several minutes ***OR***
    - ✓ 5 ml/kg of 10% dextrose by slow IV infusion ***OR***
    - ✓ For other strengths of dextrose, calculate accordingly.
- This should be followed by intravenous infusion of 10% dextrose) given slowly;
- Re-check blood glucose every 2-4 hours during the course of treatment, particularly in the pregnant or comatose patient because hypoglycemia can recur even after an IV bolus of glucose.

1.3 Seizure

- Do RBS to R/O hypoglycaemia, if there correct as mentioned above
- **Diazepam 0.15 mg/kg** maximum 10mg **IV stat** then phenytoin 20mg/kg followed by 5 mg/kg/day
- The IV diazepam can also be given **intra-rectally** using a rectal tube or NG tube **(0.5-1.0 mg/kg**) if injection is not possible.
- Diazepam can cause respiratory depression. Therefore, an Ambu bag and resuscitation equipment should be at hand when used.

1.4 Severe Anaemia

- ➢ Anemia associated with malaria is partly due to the destruction of red cells that contain parasites (hemolysis). Several other mechanisms may accelerate the development of anemia:
- ➢ non-parasitized red cells are destroyed more quickly than normal cells during malarial illness, and the bone marrow does not function adequately.
- ➢ Anemia is worsened if there is abnormal bleeding, intravascular hemolysis or renal failure

Note:

- ❖ Co-infection with other parasitic diseases (e.g. Schistosomiasis, Visceral Leishmaniasis, soil transmitted helminths) may further increase anemia.
- ❖ Only about 1/3rd of patients with mild anemia show pallor and patients may have moderate anemia without showing pallor. To confirm that anemia is present, Hb levels should be measured.
- ❖ Patients with severe anemia may present with palpitation, dyspnoea or tachypnoea. Severe or rapidly developing anemia may contribute to both cerebral signs (e.g. confusion, restlessness, coma /altered consciousness and retinal hemorrhages) and cardiac failure.

Management

- The most common indication for blood transfusion is severe anaemia.

- Assess the patient's clinical condition rather than relying on the haematocrit and/or Hb level.
- As a rule of thumb: Indication for transfusion
  - If the haematocrit is <15%
  - Anomia-associated acidosis, shock or the parasitaemia is so high that you can predict a critical drop
  - Spontaneous bleeding

1.5 Acute pulmonary oedema and ARDS

- Pulmonary edema is a grave complication of severe malaria and has a high mortality rate. It may appear several days after chemotherapy has been started and at a time when the patient's general condition is improving and peripheral parasitemia is diminishing.
- It must be differentiated from iatrogenically produced pulmonary edema resulting from fluid overload (caused by poor management of the intravenous infusion).
- ARDS appears to be due to the direct effect of parasites sequestered in the lungs, possibly through release of cytokines. It is indistinguishable for pulmonary edema but both of these complications are unusual in children.

Clinical presentation:

- Hyperventilation (rapid breathing) is the initial manifestation
- Crackles are present on auscultation, and pink frothy sputum (severe cases).

Management

- Semi-erect positioning
- Intra nasal O_2
- Fluid restriction and
- Diuretics for overhydration, e.g. furosemide 40 mg IV. If no response increase dose progressively to maximum 6mg/kg/day
- Intubation and mechanical ventilation including positive end expiratory pressure (PEEP), perform regular suction (via endo tracheal tube or oral/ naso pharangeal airway) for ARDS

1.6 Algid malaria

- **Severe malaria complicated by circulatory shock is known as algid malaria.** Which is characterized by hemodynamic disorders as shock with pronounced metabolic changes and hypothermia.
- Algid is a rare complication (0.37% of cases).

Management

- **large-volume fluid resuscitation** and hemodynamic optimization
  - The optimal resuscitation strategy for algid malaria is unknown, and volume restriction has been advocated as a means to prevent life-threatening cerebral and pulmonary oedema.
- **Early antimalarial agents** and
- **broad-spectrum antibiotics.**

1.7 Acute renal failure

- Acute renal failure — acute tubular necrosis — is a common complication in adults, but is rarely seen in children.
- It is worsened by hypovolemia and hypotension.
- It is highly preventable if fluid balance and BP is maintained. If a patient has oliguria, first correct fluid deficit and try to correct BP
- However, if there is persistent oliguria (<17 ml/hour in adults: 0.3 ml/kg/hour in children) despite adequate correction of dehydration or hypotension, renal failure is present or imminent. Hiccup may be an indicator of advanced renal failure.

Management

- Correct rehydration
- decrease IV quinine dose by 30-50 % after 2 days of Rx
- Avoid nephrotoxic drugs
- Follow input-output and serum cr
- Haemodialysis when cr > 3mg/dl

1.8 Hemoglobinuria:

- Hemoglobinuria results from the rapid breakdown of red blood cells (massive intravascular hemolysis) in the circulation.

Clinical presentation:

- The urine is dark, and tests strongly positive for blood (Hb) but contains no red cells on microscopy.
- The plasma may also be dark because of the hemoglobin released from the red cells.

Management:

- Maintain hematocrit above 15%
- monitor JVP to avoid fluid overload and hypovolaemia

- If oliguria develops and BUN & cr levels rise, consider peritoneal dialysis or hemodialysis
- continue anti-malarial therapy.

1.9 Jaundice:

- Jaundice is more common in adults than in children and is due partly to hemolysis and partly to liver dysfunction.

Clinical presentation:

- Yellowish discoloration of the sclerae of the eyes or the frenulum of the tongue is quite commonly seen in severe *P. falciparum* malaria in adults, but is uncommon in children.
- Signs of hepatic failure are rare.
- Jaundice in malaria occurs at the same time as fever, unlike jaundice due to hepatitis.
- If jaundice is present, look for other complications.

1.10 Bleeding tendency:

- In *P. falciparum* malaria, the platelet count is typically reduced. Nevertheless, spontaneous bleeding is rare in both children and adults. When it develops, it results from DIC.

Management:

- Check bleeding time of the patient, crossmatch blood, give whole fresh blood or platelet infusion as needed to correct blood loss and bleeding.

Treatments contra-indicated in the patient with severe malaria

The following treatment should not be administered to patients with severe malaria:

- ✓ Corticosteroids and NSAID (ibuprofen, aspirin);
- ✓ Other agents given for cerebral edema (urea, mannitol);
- ✓ Low molecular weight dextran;
- ✓ Epinephrine (adrenaline);
- ✓ Heparin;
- ✓ Epoprostenol (prostacyclin);
- ✓ Pentoxifylline (oxpentifylline);
- ✓ Hyperbaric oxygen;
- ✓ Cyclosporine (cyclosporin A.).

Chronic Complications of Malaria

1. Hyper reactive malarial splenomegaly (HMS)

Pathogenesis

- Abnormal immune response to repeated malarial infection
- RES hyperplasia and ↑ clearance

Presentation

- **Massive splenomegaly + peri splenitis**
- **Hepatomegaly**
- **Anaemia (NCNC) + pancytopenia**
- **Prone to skin + respiratory infection, sepsis**
- ↑ Serum titre of IgM and malarial Antibodies
- Hepatic sinusoidal lymphocytosis
- Peripheral B-Cell lymphocytosis
- Hypergammaglobulinemia
- At risk of malignant lymphoproliferative disorder

Major criteria include

- Gross splenomegaly (≥ 10 cm) below the costal margin in adults for which no other cause can be found
- Elevated serum IgM level ≥ 2 standard deviations above the local mean
- Clinical and immunologic responses to antimalarial therapy
- Regression of splenomegaly by 40% by 6 months after start of therapy
- High antibody levels of Plasmodium species (≥1:800)

Minor criteria include the following:

- Hepatic sinusoidal lymphocytosis
- Normal cellular and humoral responses to antigenic challenge, including a normal Phyto hemagglutination response
- Hypersplenism
- Lymphocytic proliferation
- Familial occurrence

Treatment

- Chloroquine 300mg po weekly for 3-6 months. Weekly and daily dosing's are said to be equally effective

2. Quartan Malarial nephropathy

- Repeated P. malariae infection → soluble immune complex deposition in glomerular BM → Nephrotic syndrome (FSGS)
- Treatment: Poorly responsive to antimalarial or steroid + cytotoxic drugs

3. Burkitt's lymphoma + EBV infection

- High prevalence in malarious areas of Africa
- Malaria induced immuno suppression may provoke EBV infection

Prevention of Malaria

- Early detection and prompt treatment of cases
- Personal protection measures: Using permethrin impregnated **bed nets** /Mosquito repellents
- **Chemoprophylaxis:** 1wk before departure and for 4 wks after leaving the endemic area. Drug options:
  - ✓ Mefloquine 228mg of base (250mg of salt) or 5 mg/kg po/week
  - ✓ Doxycycline 100mg once a day
  - ✓ Chloroquine 300mg of base orally, once\wk
  - ✓ Proguanil 200mg orally, once \day, in combination with weekly chloroquine

Special population considerations

Pregnancy

Maternal effect

- High level parasitaemia
- in low-transmission areas, the risk of development of severe malaria is high.
- Common complications: Anaemia, hypoglycaemia and acute pulmonary oedema

Fetal effects

- Fetal distress, Premature labor, Still birth, LBW

- Congenital malaria in new born

Treatment of Malaria in Pregnancy

- The **first-line treatment** for P. falciparum infection in pregnant women in the **first trimester** of pregnancy is **oral quinine** administered at 10 mg/kg salt or 8.3 mg/kg base (up to 600 mg quinine sulfate salt or 542 mg quinine base), TID, for 7 days
- AL is indicated in first trimester pregnancy only if this is the only treatment available for *P. falciparum* malaria.
- *P. falciparum* or mixed infection in **2nd or 3rd trimester** will be treated with **AL.**
- Pregnant women with only ***P. vivax*** will be treated with **chloroquine in all trimesters**
- **Primaquine is contraindicated in all trimester** of pregnancy and lactating mothers during the first 6 months
- The recommended treatment for **severe malaria** in all patients including pregnant women is **artesunate** injection, or alternatively artemether IM during the second and third trimester or alternatively quinine infusion if both of these are unavailable.
- Special precaution should be taken to prevent hypoglycaemia in pregnancy.
- **Mefloquine as prophylaxis is contraindicated** during pregnancy. Intermittent preventive treatment (IPTp) with SP is not recommended in Ethiopia.

Paediatrics

- AL is currently recommended for the treatment of uncomplicated malaria in infants under 5 kg as the same dose as 5 kg
- Chloroquine is a safe drug that can be used in all children with only P. vivax infection
- Available syrups for infants and children
  - ✓ cotexin syrup /**dihydro artemisinin/, 160mg/80ml, 4 mg/kg/day, PO, BID for 4 days** or 4 mg/kg/day, PO, BID in the 1st day followed by 2 mg/kg/day PO, BID for the next 6 days (used for all malaria subtypes)

    or you can use the following table for **dihydro artemisinin syrup**

Weight in kg	Day1 (ml, PO, BID)	Day 2 to day 7 (ml, PO, BID)
< 5	5	2.5
5 - 10	10	5
10 - 15	15	7.5
16 - 20	20	10
> 20	Tablet is recommended	

  - ✓ **Artemether syrup**

Age	Dosage (PO, BID, for 3 days)
1 - 6 months	5 ml
7months - 3yr	10 ml
4 - 8 yr	15 ml
9 - 12 yr	20 ml

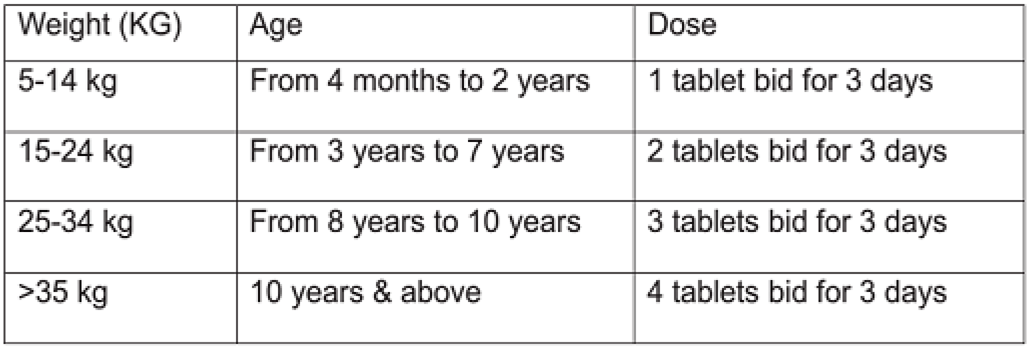
For **severe malaria in children**

- **Artesunate** 2.4 mg/kg/dose (for Children weighing > 20 kg); or 3 mg/kg/dose (for Children weighing < 20 kg), IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day for 5 days or until the patient tolerates PO medication. If the patient tolerates after 24 h, the medication can be changed to PO AL for the next 3 days.
- **under six years of age,** treat with a single dose of rectal artesunate (10mg/Kg) and immediately go to appropriate further care. Do not use rectal artesunate in older children and adults.

☛ **Refer Updated National paediatric malarial infection guideline**

Antimalarial drugs (Dose and special considerations)

A. Coartem (AL)



Weight (KG)	Age	Dose
5-14 kg	From 4 months to 2 years	1 tablet bid for 3 days
15-24 kg	From 3 years to 7 years	2 tablets bid for 3 days
25-34 kg	From 8 years to 10 years	3 tablets bid for 3 days
>35 kg	10 years & above	4 tablets bid for 3 days

Contraindications:

- ✓ Pregnant women in the first trimester
- ✓ Persons with a previous history of reaction after using the drug;
- ✓ Persons with severe and complicated malaria should not be treated with oral medications.

B. Chloroquine Treatment Schedule

- Chloroquine is available as tablet (250 mg, which is equal to 150 mg base) or as syrup (50 mg base per 5 ml).
- The dose is 10 mg base/kg/day, PO, TID, 1st and 2nd days, and 5mg base/kg/day, PO, TID, on 3rd day for 3 days (for a total dose of 25 mg chloroquine base/kg with a maximum total of 1,500 mg chloroquine base /= maximum of 2,500 mg chloroquine phosphate salt/).

Contraindications:

- ✓ persons with known hypersensitivity
- ✓ persons with a history of epilepsy
- ✓ persons suffering from psoriasis

C. Primaquine phosphate

- **dose: 0.25 mg base per kg daily for 14 days for *P. vivax* (single dose primaquine for *P. falciparum* cases)**

Contraindications:

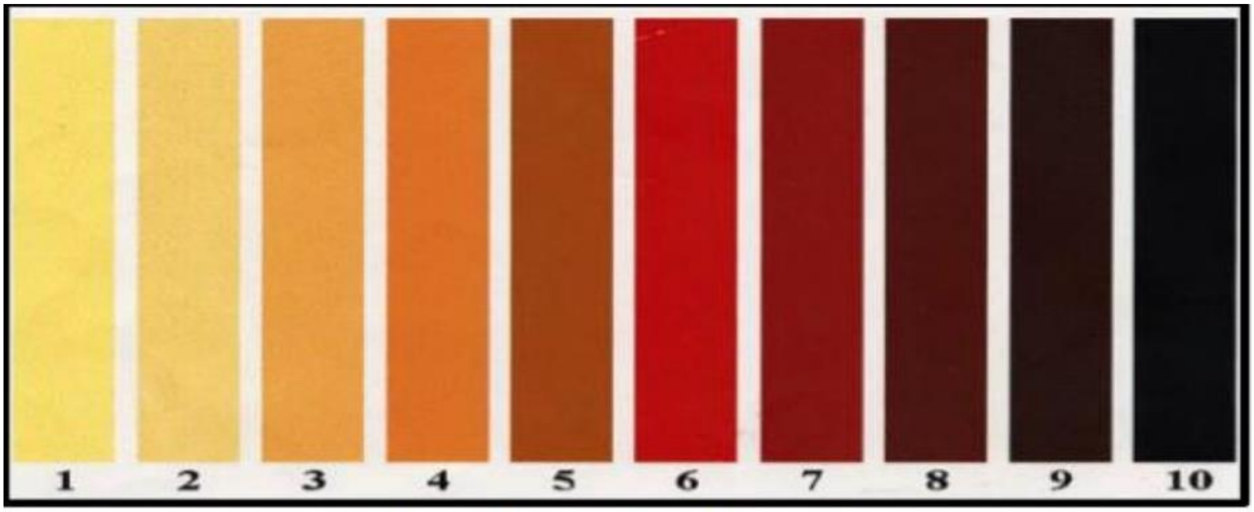
- ✓ Pregnancy
- ✓ In breast feeding mothers less than six months infants
- ✓ Infants under six months
- ✓ Any condition that predisposes to granulocytopenia, such as active RA & SLE

When to stop Primaquine

- ❖ Symptomatic anemia
- ❖ Urine color: a score of 5 or above on the Hillmen urine colour chart
- ❖ Hemoglobin < 5 g/dL
- ❖ Hemoglobin drop of >50% of the baseline
- ❖ Hemoglobin < 7 g/dL AND Hemoglobin drop from baseline of >25%

Hillmen urine color estimation for haemoglobinuria:

- urine should be placed in a clear glass container and held up against a white piece of paper, in a well illuminated area, before estimating the colour compared to the Hillmen Colour Chart.
- Urine colour estimation should be carried out as soon after voiding as possible.
- A score of 5 or above is considered evidence of haemoglobinuria.



Hillmen Urine Colour Chart

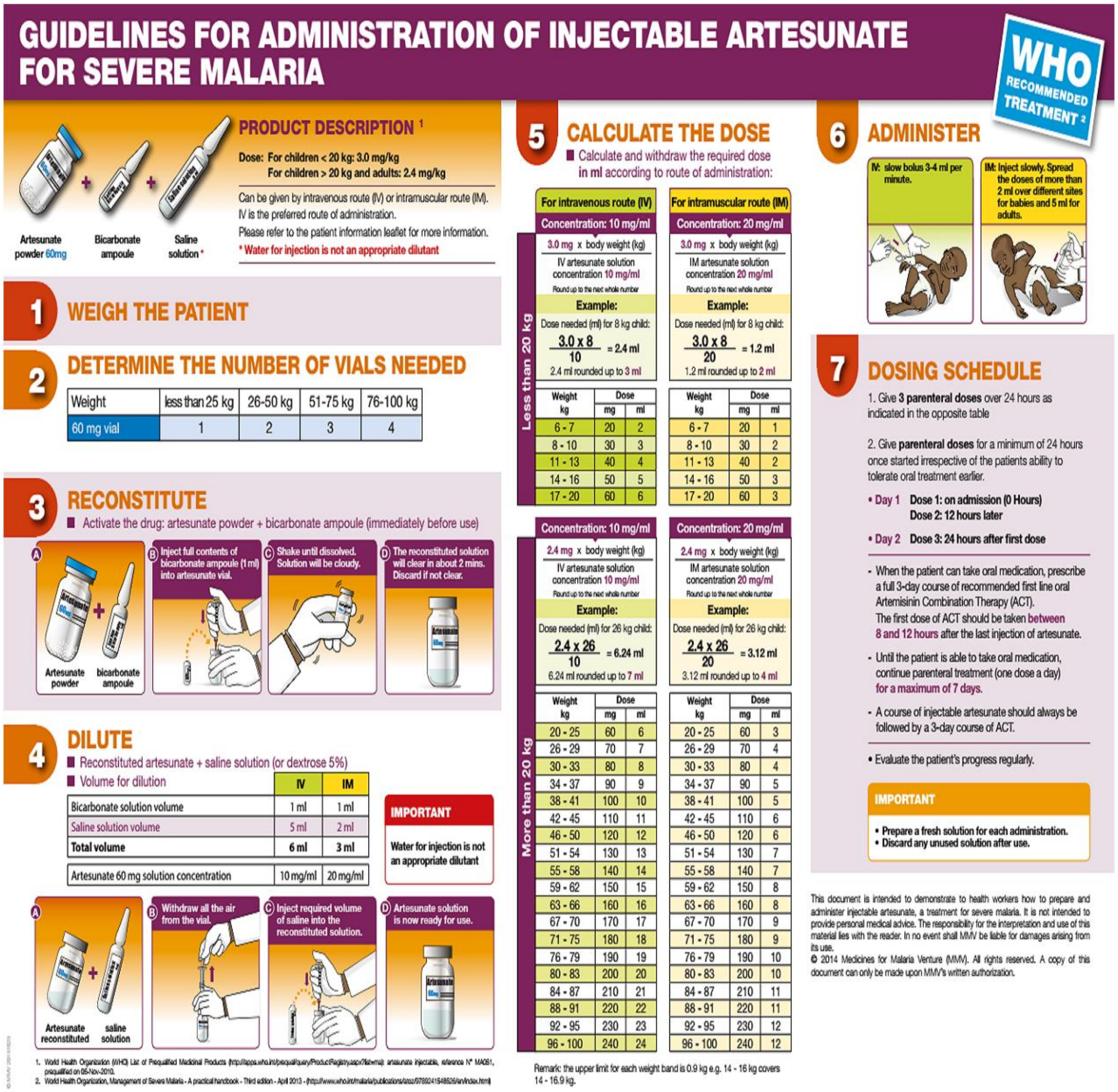
Procedure

- ✓ The day of initial treatment is designated as day zero. The patient will be seen at the health facility at days 3, 7 and 13 to check symptoms of anemia, urine color and hemoglobin measurement.
- ✓ Ask for anemia symptoms at each visit.
- ✓ Measure hemoglobin on days 0, 3, 7 and 13

D. ORAL QUININE TREATMENT SCHEDULE

- Oral quinine dosage is 8.3 mg base/kg (=10 mg quinine sulphate salt/kg), TID, for 7 days. (The maximum adult dose is 600mg quinine sulphate (salt), TID, for 7 days.)

E. Artesunate Injection for severe malaria



GUIDELINES FOR ADMINISTRATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA

WHO RECOMMENDED TREATMENT[2]

PRODUCT DESCRIPTION[1]

Artesunate powder 60mg + Bicarbonate ampoule + Saline solution*

Dose: For children < 20 kg: 3.0 mg/kg
For children > 20 kg and adults: 2.4 mg/kg

Can be given by intravenous route (IV) or intramuscular route (IM).
IV is the preferred route of administration.
Please refer to the patient information leaflet for more information.
* Water for injection is not an appropriate dilutant

1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE

- Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)

Ⓐ Artesunate powder + bicarbonate ampoule
Ⓑ Inject full contents of bicarbonate ampoule (1 ml) into artesunate vial.
Ⓒ Shake until dissolved. Solution will be cloudy.
Ⓓ The reconstituted solution will clear in about 2 mins. Discard if not clear.

4 DILUTE

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	**6 ml**	**3 ml**
Artesunate 60 mg solution concentration	10 mg/ml	20 mg/ml

IMPORTANT

Water for injection is not an appropriate dilutant

Ⓐ Artesunate reconstituted + saline solution
Ⓑ Withdraw all the air from the vial.
Ⓒ Inject required volume of saline into the reconstituted solution.
Ⓓ Artesunate solution is now ready for use.

5 CALCULATE THE DOSE

- Calculate and withdraw the required dose **in ml** according to route of administration:

Less than 20 kg

For intravenous route (IV) — Concentration: 10 mg/ml

$$\frac{3.0 \text{ mg} \times \text{body weight (kg)}}{\text{IV artesunate solution concentration } 10 \text{ mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{10} = 2.4 \text{ ml}$$

2.4 ml rounded up to 3 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

For intramuscular route (IM) — Concentration: 20 mg/ml

$$\frac{3.0 \text{ mg} \times \text{body weight (kg)}}{\text{IM artesunate solution concentration } 20 \text{ mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{20} = 1.2 \text{ ml}$$

1.2 ml rounded up to 2 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

More than 20 kg

IV — Concentration: 10 mg/ml

$$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{\text{IV artesunate solution concentration } 10 \text{ mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{10} = 6.24 \text{ ml}$$

6.24 ml rounded up to 7 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

IM — Concentration: 20 mg/ml

$$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{\text{IM artesunate solution concentration } 20 \text{ mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{20} = 3.12 \text{ ml}$$

3.12 ml rounded up to 4 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Remark: the upper limit for each weight band is 0.9 kg e.g. 14 - 16 kg covers 14 - 16.9 kg.

6 ADMINISTER

IV: slow bolus 3-4 ml per minute.

IM: Inject slowly. Spread the doses of more than 2 ml over different sites for babies and 5 ml for adults.

7 DOSING SCHEDULE

1. Give **3 parenteral doses** over 24 hours as indicated in the opposite table

2. Give **parenteral doses** for a minimum of 24 hours once started irrespective of the patients ability to tolerate oral treatment earlier.

- Day 1 **Dose 1: on admission (0 Hours)**
  Dose 2: 12 hours later
- Day 2 **Dose 3: 24 hours after first dose**

- When the patient can take oral medication, prescribe a full 3-day course of recommended first line oral Artemisinin Combination Therapy (ACT). The first dose of ACT should be taken between 8 and 12 hours after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) for a maximum of 7 days.
- A course of injectable artesunate should always be followed by a 3-day course of ACT.

- Evaluate the patient's progress regularly.

IMPORTANT

- **Prepare a fresh solution for each administration.**
- **Discard any unused solution after use.**

This document is intended to demonstrate to health workers how to prepare and administer injectable artesunate, a treatment for severe malaria. It is not intended to provide personal medical advice. The responsibility for the interpretation and use of this material lies with the reader. In no event shall MMV be liable for damages arising from its use.

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1. World Health Organization (WHO) List of Prequalified Medicinal Products (http://apps.who.int/prequal/query/ProductRegistry.aspx?list=ma): artesunate injectable, reference N° MA051, prequalified on 05-Nov-2010.
2. World Health Organization, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - (http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html)

F. **Artemether injection**

- Artemether injection is given at a loading dose of 3.2 mg/kg on the first day followed by 1.6 mg/kg daily for two days. Then if the condition of the patient improves, will be followed by full dose AL

Relative Contraindications:

- ✓ IM Artemether should only be used during the first trimester of pregnancy when IV/IM artesunate (preferred) and IV/IM quinine are both unavailable.

3.10.2 Typhoid fever (ታይፎይድ)

Salmonellosis

- Caused by the genus Salmonella → Non spore-forming gram -ve bacilli
- Enteric fever
  - Clinically the most important form
  - Caused by:
    - Salmonella enterica serotype Typhi (formerly S. typhi) — Causes typhoid fever
    - Salmonella enterica serotypes Paratyphi A, B and C (formerly S. paratyphi A, B and C) — Cause paratyphoid fever

Typhoid fever

- Typhoid fever is an acute febrile illness caused mainly by *Salmonella typhi*. The mode of transmission is via contaminated food or water.
- Clinically the term includes the milder paratyphoid fever
- Common in countries with poor access to sanitation

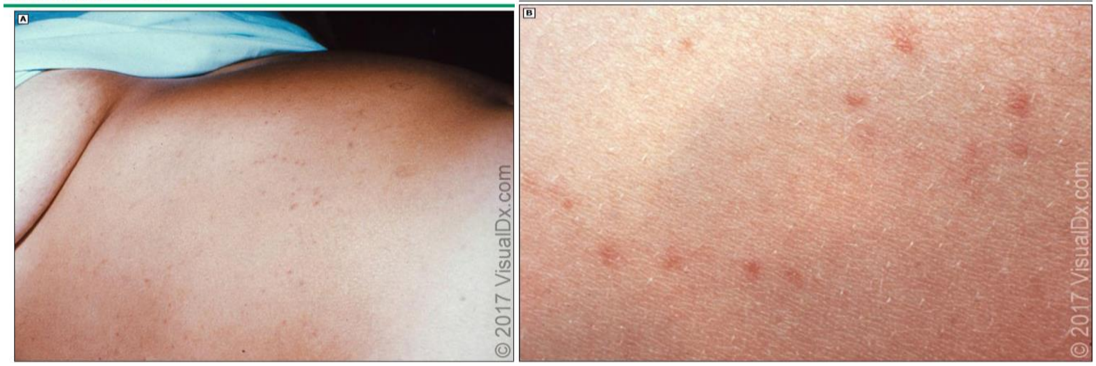
Pathogenesis:

- Ingestion of contaminated food or drink → penetration of gut mucosa → infection of lymphoid tissues → lymphatic/hematogenous dissemination and colonization of RES → infection of body parts/ re-infection of intestine

Clinical presentation

  - ✓ IP: 3 to 21 days
- Fever and abdominal pain
- Diarrhoea (children, HIV infected, malnourished patients) or constipation (adults)
- Skin rashes (rose spots)
- Hepatosplenomegaly
- Delirium, coma

Rose spots of typhoid fever



Rose spots are small (1 to 5 mm), erythematous, blanchable, nontender papules, which begin early during the acute febrile period of typhoid fever. Crops of lesions (10 to 20) appear at irregular intervals for approximately 10 to 14 days, typically distributed on the abdomen, chest, and back. Rarely, vesicular or hemorrhagic lesions appear. The lesions persist for two to three days.

Clinical features based on onset of illness

- 1st week
    - Stepp ladder fever, chills and rigor
    - Malaise
    - Headache
    - Joint pain
- 2nd week
    - Abdominal pain
    - Diarrhoea or constipation
    - Skin rashes (rose spots)
- 3rd week
    - Hepatosplenomegaly
    - GI bleeding
    - Intestinal perforation (severe abdominal pain)

- **N.B these features are not always present. But fever is always there the name so called typhoid fever**

Complications

- Intestinal perforation/ bleeding
- Hepatic/ splenic abscesses
- Meningoencephalitis, nephritis, arthritis, osteomyelitis

- Relapse rate after Rx is 10%
- Chronic carriers: asymptomatic individuals who shed the organisms (in urine or stool) for more than 1 year
    - ✓ Mainly: women, patients with biliary stones or tumors, GI malignancy

Diagnosis

- Diagnostic gold standard: Mnemonic → culture from BUS (Blood, BM, urine or stool) samples
  - Blood culture ---best in the 1st week (90% Sensitivity); less so in the 3rd week (50% Sensitivity)
  - BM culture — especially in those who took antibiotics for < 5 days
  - Stool and urine cultures — best in the 3rd week in untreated patients
- **Serological examination**, such as the **Widal test** may be used as an adjunt to diagnosis in the proper clinical setup particularly in children < 10 years old and travellers from nonendemic areas. **The Widal test is, however, characterized by false positive results. But we are using it currently in our set up**
  - ✓ The Widal test detects anti-*S*. Typhi antibodies, and the minimal titers defined as positive for the **O** (surface polysaccharide) antigens for **active infection** and H (flagellar) antigens in past infection or in immunized person.

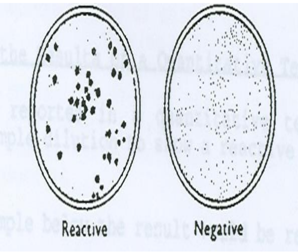
Limitation of widal test

False positive reactions

- Due to past infection
- Cross reaction (malaria, relapsing fever, non-typhoidal salmonella)

False negative reaction

- Early typhoid cases
- Poor antigen preparation
- Poor transport of reagents &storage.



Widal test; rapid slide test

- For more about widal test click here → widal test

- CBC
  - ✓ Patients with enteric fever frequently have **anemia and either leukopenia or leukocytosis**

- ✓ **leukopenia with left shift** is typically seen in **adults**, while leukocytosis is more common in children.
- ✓ leucocytosis in the 3rd week of illness, should prompt suspicion of intestinal perforation.
- ❖ Deranged OFTs

Management

Symptomatic treatment:
Use of antipyretics, e.g. paracetamol to control fever.

Uncomplicated Typhoid fever

First line

- ✓ Ciprofloxacin, 500mg P.O., BID for 7 to 10 days

Alternative

- ✓ Azithromycin,1g, PO, daily for 5 to 7 days
- ✓ Cefixime, 400mg, PO, daily for 7 to 14 days

- N.B local studies in Ambo and Mekelle, showed that **50-100%** of isolates were **resistance to previously recommended antibiotics like amoxicillin, cotrimoxazole**, erythromycin, Nitrofurantoin, streptomycin and doxycycline, and **20% for chloramphenicol.**
  - ☛ Thus, the main options are fluoroquinolones, 3rd generation cephalosporins, and azithromycin.

Complicated/ severe Typhoid fever

- For patients who have severe disease (e.g. systemic toxicity, depressed consciousness, prolonged fever, organ system dysfunction, or other feature that prompts hospitalization) and complication, initial therapy with a parenteral agent is appropriate.

First line

- ✓ Ceftriaxone 1g, IV/IM, daily or in 2 divided doses, for 10 - 14 days

Alternative

- ✓ Cefotaxime, 1 - 2 g, IV, TID, for 10 - 14 days

- ✓ ?? Chloramphenicol, 1g, IV, QID, until 48 hrs after fever has settled,
  followed by 500mg P.O., QID for a total of 14 days.

Adjunct Corticosteroid treatment:

- This is recommended only for patients with evidences of CNS involvement
  (delirium, obtundation, stupor, coma) or shock

First line

- ✓ Dexamethasone, 3mg/kg IV initially, followed by 1mg/kg IV QID, for
  48hrs total (This is preferred in patients with severe disease)

Alternative

- ✓ Prednisolone, 20-40mg P.O., (or equivalent) once daily for the first 3
  days of antibiotic treatment.

Special population considerations

Paediatrics:

- fluoroquinolone use is not justified in paediatrics <18 years old due to arthropathy and cartilage toxicity in immature animal studies.
  - ☛ Hence only recommended for sever enteric fever if and only if there are no other alternatives (use Ciprofloxacin 15mg /kg /dose, BID, for 7-10 days).

First line (3rd Generation Cephalosporin)

- ✓ Cefixime, 15 to 20 mg/kg/day (max; 400 mg/day), PO, BID, for 7 to 14 days; (available syrups 100mg/5ml, 200mg/5ml, 500mg/5ml) OR
- ✓ Ceftriaxone, 80 mg/kg/day, IV, daily for 7 to 14 days OR
- ✓ Cefotaxime, 150 - 200 mg/kg/day in 3 to 4 divided doses (max: 12 g daily), IM/IV, for 7days
  - For fluoroquinolone resistant: 80 mg/kg/day in 3 to 4 divided doses (max: 12 g daily)

Alternatives (not effective)

- ✓ ??? Azithromycin (syrup 200mg/5ml), 20 mg/kg/day, PO, daily for 5 to 7 days
- ✓ ??? Cefaclor, 20 to 40 mg/kg/day, BID or TID, for 7 days
- ✓ ??? Cephalexin (syrup 125mg/5ml, 250mg/5ml), 50mg/Kg/day, BID for 7days

Pregnant women:

- Fluoroquinolone are contraindicated in pregnant mothers.
- Third generation cephalosporins should be used in pregnant mothers in place of fluoroquinolone or azithromycin.

First line

- ✓ Ceftriaxone 1g, IV/IM, daily or in 2 divided doses, for 7 days

Alternative

- ✓ Cefotaxime, 1g, IV, TID, for 7 days

3.10.3 Typhus (ታይፈስ)

- Typhus is a disease Caused by Rickettsiae
- Commonly there are two types of epidemiologically distinct typhus.

	Epidemic typhus	Endemic typhus
Another name	louse-borne typhus	flea-borne typhus
Caused by	R.prowazekii	R.typhi
Transmitted by	body louse	Tick
Vectors	Pediculus humanus corporis	Fleas
Reservoirs	---	Rats

- Other strains of rickettsia are also present in Ethiopia.

1. Epidemic Typhus

Epidemiology:

- Currently prevalent in mountainous areas of Africa, South America and Asia
- Persist and common in the rugged, mountainous areas of Ethiopia
- Particularly high during the rainy seasons from July to September and December.

- It is related to poverty, war and disasters and common among a crowded, cold, and unhygienic environments (e.g. rural communities, day laborers, and homeless people). Hence, typhus is probably common across the country.
- Lice acquire the organism when they ingest a blood meal from a rickettsemic patient

Transmission

- Rickettsiae multiply in the mid-gut of lice
- Infected lice defecate during blood meal, and the patient auto inoculates the organisms by scratching

- **Brill-Zinser disease** is a recrudescent, mild form of epidemic typhus occurring years after the acute disease, probably as a result of immunosuppression or old age
- Potential agent of bioterrorism
    - high case fatality rate
    - difficult to diagnose
    - inhalation of aerosols is highly infectious

2. Endemic Typhus

Transmission:

- ✓ Fleas acquire R. typhi from rickettsemic rats and humans are infected when rickettsia-laden flea feces are “scratched” into pruritic bite lesions
  and infrequently by direct flea bite
- ✓ Inhalation of aerosolized flea feces can transmit the infection

Clinical Manifestations of typhus

The clinical presentation of both types is similar and cause an AFI characterized by:

- ✓ IP: 1 to 2 weeks
- ✓ Prodromal symptoms: headache, myalgia, arthralgia, nausea and malaise
    - Followed by abrupt onset of fever (>38°C), chills, maculopapular rash

- Rash
  - Usually starts on the 5th day
  - Macular, maculopapular, petechial
  - Initially on the trunk -> then becomes generalized
  - Spares face, palms and soles
- ✓ Pulmonary involvement is frequently prominent
  - Dry cough, bibasilar rales
  - CXR: interstitial pneumonia, pulmonary edema, pleural effusion
- Tachycardia
- Hypotension
- Less commonly: abdominal pain, Eye pain, confusion, stupor, seizures, ataxia,
coma, photophobia, jaundice, conjunctival injection, Splenomegaly

CXN of typhus

- Vasculitis resulting in gangrene and cerebral thrombosis is among the more serious complications of typhus.
- Skin necrosis and gangrene of the digits
  - ✓ Respiratory failure
  - ✓ Hematemesis
  - ✓ Cerebral hemorrhage
  - ✓ Greater severity is associated with old age, underlying disease and treatment with sulfa drugs
  - ✓ Case fatality rate in untreated patients: 1%, may reach up to 40%

Diagnosis of typhus

- The Weil Felix serology test with demonstration of a rising/high titer.
  - For more about Weil Felix serology test click here → Weil-Felix slide agglutination test
- IFA (Micro immunofluorescent) and plate microagglutination tests have high sensitivities for typhus
- Immunohistology of skin biopsy
- PCR

Treatment of typhus

Non pharmacologic

- ✓ Delousing:
  - ➢ Regularly washing clothes and body plus long-acting insecticides should be used.
  - ➢ Pyrethroid permethrin is the delousing agent of choice. It can be applied as a dust or spray to clothing or bedding.

Pharmacologic

☛ Identification of the etiology is highly challenging. Hence, empiric therapy for this AFI should carefully consider the patient clinical presentation, the local typhus epidemiology, and the population group seeking care (e.g. homeless, poor hygienic ore recent travels to rural areas where louse born case are dominant).

First line

- ✓ **Doxycycline**, 100mg, PO, BID (200mg, P.O., daily) for 7-10 days OR
- ✓ **Tetracycline**, 250mg, P.O., QID for 7-10 days

Alternatives

- ✓ **Chloramphenicol, 500**mg P.O., QID for 7 days
  - ▪ for children: 25mg/kg

☛ **The alternative drug is Used** In patients allergic to Tetracyclines, in reduced renal function, in pregnant women, and in children younger than 8 years of age who require prolonged or repeated courses of therapy

Prevention

- ➢ **Delousing**:
- ➢ **Antibiotic prophylaxis**:
  - ▪ Doxycycline 200mg PO stat.
  - ▪ For travelers to endemic areas a weekly single dose for the duration of stays and continued for one week after leaving the area can be used.
- ➢ **Environmental control**: Areas where flying squirrels are common like in campgrounds, roof joists, etc. should be sealed with metal screening to prevent squirrels from nesting in inside homes or around human residency areas.
- ➢ No specific vaccine is on use currently.

Special population considerations

Pediatrics:

- ✓ Tetracyclines should not be used in children less than 8 years.
- ✓ CDC recommends **“doxycycline as first line choice for children of all ages** with suspected tickborne rickettsial disease.
- ✓ In premature and full-term neonates **CAF will result in “gray baby syndrome"** characterized by cyanosis, abdominal distention, vasomotor collapse, and death due to poor metabolism potential of the infants.

Pregnant women:

- ✓ **Tetracyclines** should not be used in pregnant mothers (it is **CAT X drug**).

3.10.4 Relapsing fever

- ❖ An acute febrile illness caused by spirochetes of the genus Borrelia
- ❖ Episodes of fever that accompany spirochetemia
- ❖ Arthropod-borne infection with two forms:
  - Tick-borne relapsing fever (TBRF)
    - Caused by B. hermsii, B. turicatae (New World species) or B. duttonii (Old World species)
    - Sporadic cases or small outbreaks
  - Louse-borne relapsing fever (LBRF)
    - Caused by B. recurrentis
    - Mainly in developing countries
    - In Ethiopia the endemic form is a louse-borne disease (LBRF)
    - Typically occurs in an epidemic form
- ❖ Borrelia are:
  - o Spirochetes morphologically different from gram positive and gram negative organisms
- ❖ Other spirochetal diseases
  - o Syphilis
  - o Leptospirosis
  - o Lyme disease

Tick borne relapsing fever (TBRF)

- ➢ Less common in the tropics
- ➢ Soft ticks (Ornithodoros spp.) transmit the infection via saliva or excretory fluid when feeding

Louse borne relapsing fever (LBRF)

- Common in the highlands of Ethiopia
- Human lice transmit the disease
- Outbreaks during cold seasons
- Also seen: during wars, famine; among refugees and homeless people
- Infected lice contain organism in their hemolymph -> infect humans when lice are crushed and fluid contaminates mucous membranes or skin abrasions

- After infection spirochetes enter the blood and are spread to different sites: liver, spleen, CNS, bone marrow, etc.
- Severity of illness depends on the density of spirochetes in the blood

Clinical manifestations

- LBRF and TBRF are similar in their manifestations
- IP: 3 to 12 days
- High grade recurrent fever is the typical feature
- Others:
  - nausea, vomiting, chills, rigors, sweating, headache, arthralgia, myalgia
- Neurologic manifestations:
  - delirium, stupor, coma, focal neurologic deficit
- Cardiopulmonary:
  - myocarditis, cough, respiratory distress
- Hematologic: bleeding

Physical examination:

- hepatosplenomegaly, cranial nerve palsies, petechiae, etc.

Diagnosis

Relapsing fever should be considered if two of the following criteria fulfilled

i. The presence of relapsing fevers, especially if the recurrent fevers are accompanied by the crisis phenomenon (rigors, further elevation of temperature, pulse and blood pressure before fever ends, for 15-30 minutes).
ii. History of exposure to, body lice in areas where louse-borne relapsing fever (LBRF) or cattle ticks in localities where tick-borne relapsing fever (TBRF) is common.

- Confirm suspicion by:

  - Blood film -> Giemsa or Wright stain -> look for extracellular Borrelia
  - PCR: done when BF is negative
- CSF analysis → If neurologic involvement suspected (meningitis or meningoencephalitis)
- In complicated cases: CBC, Liver function tests, ECG
- Culture and serology mostly not applicable

Management

Non pharmacologic

- ❖ Delousing

Pharmacologic

First line

- ✓ **Procaine penicillin**, 400,000-800,000-unit I.M. stat.
  - For children: 200,000-400,000 units.
- Check blood film after 12 hours of treatment.
  - If negative → give tetracycline 250 mg TID for 3 consecutive days.
  - If the blood film remains positive → repeat the same dose of procaine penicillin and continue with tetracycline later as described above.

Alternative

- ✓ **Tetracycline hydrochloride**, 500mg P.O. daily for 2 days. *OR*
- ✓ **Erythromycin,** 500mg P.O., stat.

Prevention

- **Reducing louse and tick exposure**:
- Good personal hygiene, reduced crowding, access to fresh water and washing facilities.
- **Post exposure antibiotic prophylaxis**:
  - doxycycline 200mg on the first day, then 100 mg/day for 4 days (1st line).
  - Tetracycline 500 mg QID for 4 days (alternative).
- No effective vaccine for relapsing fever.

Special population considerations

Pediatrics:

- ✓ **Tetracyclines are contraindicated in children less than 8 years.**
- ✓ In premature and full-term **neonates CAF will result in "gray baby syndrome"** characterized by cyanosis, abdominal distention, vasomotor collapse, and death due to poor metabolism potential of the infants. Hence, penicillin, macrolides and cephalosporins can be used.

Pregnant women:

- ✓ Tetracyclines should not be used in pregnant mothers.
- ✓ Penicillin, macrolides and cephalosporins can be used in pregnant and nursing mothers.

N.B.

1. Jarish-Herxheimer reaction:

- ❖ Some patients may develop Jarisch-Herxheimer reaction and is believed to be due to a rapid clearance of the spirochetes.
- ❖ The first dose of appropriate antibiotic causes transient worsening of clinical symptoms/signs. This mostly happens within the first two hours after antibiotic administration.
- ❖ This reaction is very common occurring in 35-100% and is associated with increased mortality.
- ❖ In its classic form, it occurs in two distinct phases:
  - ✓ **Chills phase** → which consists of a rise in BP, pulse, and respiratory rate; and
  - ✓ **flush phase** → which is associated with dramatic fall of BP.
- ❖ The reaction should be actively anticipated and managed aggressively with fluid resuscitation and cardiovascular support

2. In patients who remain febrile after treatment, consider other concomitant infections like typhus.

3.11 MSS Related disorders and infections

3.11.1 Rheumatologic Disorders

3.11.1.1 Gout (ሪህ)

- Gout is a common inflammatory arthritis resulting from deposition of crystals of urate in the joint space and tissues around the joint.
- Urate crystals are formed as a consequence of long term elevation of serum uric acid levels in a predisposed individual.
- Uric acid is a byproduct of purine metabolism. Most of the purine is produced endogenously by the liver and a lesser part comes from consumption of purine rich food.
- Recurrent gout attack can cause joint damage, additionally it can result in:
  - Tophus (pleural form, Tophi): accumulation of urate crystals in subcutaneous tissue, cartilage and soft tissue areas.
  - Kidney stones: formation of urate stones in the kidneys and urinary tract
  - Urate Nephropathy
- Although the prevalence of gout is not studied in Ethiopia, it is one of the commonest causes of inflammatory arthritis observed in clinical practice.

Risk factors for Gout

- Obesity
- Hypertension
- DM
- Metabolic syndrome
- CKD
- Alcoholism

- **Males are much more commonly affected than females.** It is rare to find gout in reproductive age woman, **after menopause the difference between men and women narrows.**
- Even though hyperuricemia is the cause gout, only 10-15% of patients with hyperuricemia develop gout.
- Most patients with hyperuricemia don’t develop clinical Gout in their life time. Due to this fact hyperuricemia should not be considered equivalent to Gout.

Clinical features

- The clinical manifestations of Gout are classified in to three
  1. Acute attacks (flares)

2. Inter critical gout (periods between flares)
3. Chronic Gout (Chronic Gouty arthropathy) with or without tophi

A. Acute attacks (flares)

Symptoms

- Severe (excruciating) pain over a joint associated with swelling, redness, and hotness.
- The pain is acute in onset and reaches to its maximum within 6-12hours, not exceeding 24hours.
- Initial attacks involve a single joint. Rarely multiple joints may be involved.
- The majority of the first attacks involve the base of the great toe (known as podagra) or knee.
- Flares usually subside within several days without treatment and few days with treatment.
- Patients might perceive the initial attack as an unnoticed trauma.
- The course of gout after the first attack is variable. Some might have no recurrence while other might have frequent or occasional recurrences.
- Multiple joint involvement and upper extremity involvement at initial presentation should prompt investigation for other causes of polyarthritis.
- Most patients do not have any symptoms in the period between flares.

Signs

- A swollen, tender, erythematous joint and evidence of joint effusion.

B. Inter critical gout (periods between flares)

- Even after a severe flare most patients enter in to a completely asymptomatic period.
- The presence of a completely asymptomatic period is unusual in other causes of arthritis, hence helps for diagnosis.

C. Chronic Gouty arthropathy/ Tophaceous gout

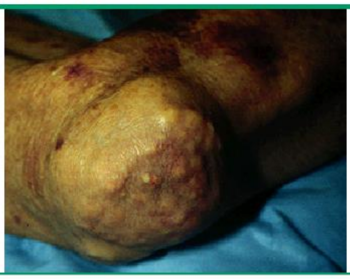
Symptoms

- Chronic joint pain of variable severity involving few or many joints
- Acute flares of variable frequency on top of chronic joint pain
- Deformity of joints with limitation of movement

Signs

- Joint deformity and swelling
- Tophi
    - Painless (non-tender), visible and palpable swelling usually present around the joints, tendons or the ears.
    - When tophi stretch the skin their white to yellow color might be visible

Tophus of the knee



Large tophus and multiple superficial tophi of the knee in patient with uncontrolled gout.

Investigation and diagnosis

Diagnosis of gout flare

- Clinical dx

clinical diagnostic rule

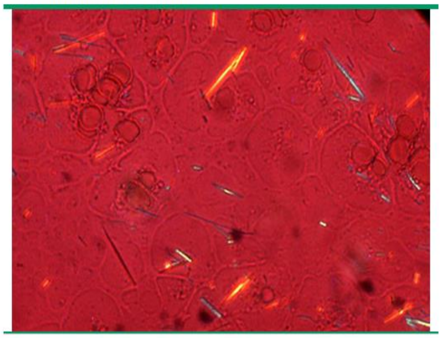
1. Male sex (2 points)
2. Previous patient-reported arthritis flare (2 points)
3. Onset within one day (0.5 points)
4. Joint redness (1 point)
5. First metatarsal phalangeal joint involvement (2.5 points)
6. Hypertension or at least one cardiovascular disease (1.5 points)
7. Serum urate level > 5.88 mg/dL (3.5 points)

Based upon the total score, patients can be identified as having **probability of gout** as;

- low (≤4 points),
- intermediate (>4 to <8 points)
- high (≥8 points)

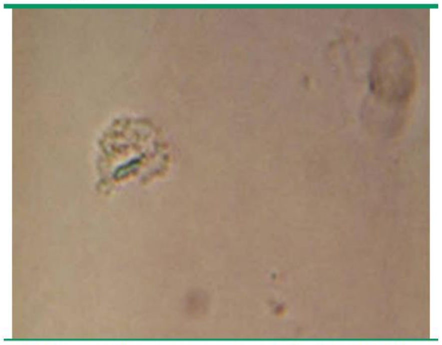
- Demonstration of urate crystals from aspirated joint fluid using polarized light microscope → Gold standard

Monosodium urate crystals



Synovial fluid from a patient with acute gouty arthritis, when viewed with compensated polarized microscopy, reveals needle-shaped, birefringent crystals. These monosodium urate crystals are bright yellow when aligned with the axis of the compensator.

Calcium pyrophosphate crystals in synovial fluid



An intracellular calcium pyrophosphate crystal is shown, which is pale blue when aligned with the axis of the compensator on polarized light microscopic examination. Note the rhomboid shape of the calcium-pyrophosphate crystal.

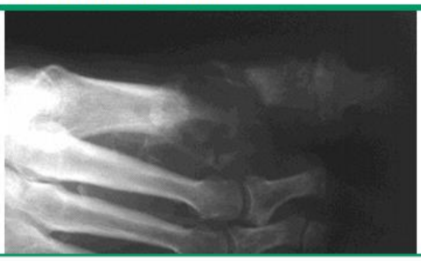
- Joint fluid aspiration and analysis is mandatory if septic arthritis is considered.

- Serum uric acid level
    - Normal or low uric acid is common during acute attacks (it can be high, normal or low).
- In acute attacks imaging (like X-ray) has limited role

Diagnosis of inter critical and chronic gout

- The diagnosis of inter critical and chronic gout depends on clinical, serum uric acid and imaging findings
    - The presence of recurrent flares and asymptomatic period
    - Presence of tophi
    - Elevated serum **uric acid level**
    - **X-ray**:
        - ✓ punched out lesion
        - ✓ intra-osseous lesions
        - ✓ sclerotic overhanging edges
        - ✓ joint space is preserved and narrowing occurs late.
        - ✓ Calcified tophi on soft tissue and joint area

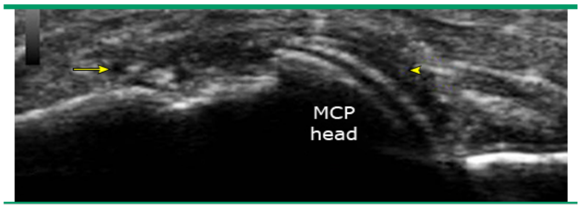
Gout of the foot radiograph



Plain radiograph of the foot demonstrating features consistent with gout. There is soft tissue swelling and extensive erosions involving the first MTP joint, as well as calcifications within a tophus.

- **Ultrasound of joint/s:**

Ultrasound of gout of the metacarpophalangeal joint



This longitudinal dorsal ultrasound scan of the second MCP joint shows thickened synovium with hyperechoic deposits (arrow) indicative of urate crystal deposition. The double contour sign at the metacarpal head (arrowhead) represents crystal deposition on the articular cartilage surface. The findings in this 56-year-old man with polyarthritis are consistent with gout.

MCP: metacarpophalangeal.

- **Evaluation of associate risk factors**→ All patients with gout need to be screened for cardiovascular risk factors:
  - ✓ FBS and/or HbA1c,
  - ✓ lipid profile
  - ✓ BUN & creatinine.
- Neutrophilic leukocytosis and/or elevation of ESR or CRP are common in gout flares, but their presence in other acute arthritides generally makes these findings of little diagnostic value.

Treatment of gout

Pharmacologic management

1. Treatment of acute attacks (flares)

First line treatment for acute attacks

A. In individuals with **normal kidney function**: NSAIDS

- **NSAIDS should be avoided in patients with impaired kidney function, active PUD and cardiovascular disease.**
- Full anti-inflammatory dose needed
- There is no evidence to show one NSAID is clearly superior to another.

NSAIDs	Dosage	Duration	Precautions
Indomethacin	Oral: 50mg, TID (Max,200mg/day)	Total duration x 7 days The initial high dose can be reduced after 2-3 days	PPI prophylaxis should be given for prevention of GI bleeding in the following group ❖ Age ≥60 ❖ Dyspepsia history in any age group ❖ Concurrent use of Aspirin, anticoagulant or steroid
	Rectal suppository: 100mg/day		
Diclofenac	Oral: Immediate release 50mg, TID Extended release 75mg, BID Maximum dose: 150mg/day		
	Rectal suppository: 100mg/day		
	Intramuscular: 75mg, IM, BID		
Ibuprofen	800mg PO TID (Max;3,200mg/day)		
Meoxicam	15mg/day, PO (Max;15mg/day)		

B. In individual with **impaired kidney function**: short course **steroids are first line**

- Prednisolone, 30mg per day, to be tapered over 10-14 days.
  - ❖ Typical prescription: 30mg x3days, 20mg x3days, 10mg x3days, 5mg x3days

Intramuscular steroid/Intra-articular steroid: If oral prednisolone is not tolerated

- Triamcinolone acetonide 40-60mg, IM, stat.
  - ❖ For intra-articular 40mg for large joints and 20mg for small joints.
- Methylprednisolone 40-80mg, IM, stat.
  - ❖ For intra-articular 40mg for large joints and 20mg for small joints, intra-articular, once

C. In patients with **diabetes**; worsening of hyperglycemia should be anticipated and doses of diabetes medication needs to be adjusted accordingly.

2. Second line treatment for acute attacks

- In normal kidney function: **Colchicine**
  - ❖ Colchicine: Initial dose of 1.2 mg, after one hour 0.6 mg, a total dose in the first day
    - ✓ Subsequent dose: 0.5 to 0.6mg daily to twice daily
    - ✓ Duration: Until symptoms subside

3. Urate lowering therapy:

- for prevention of recurrence, joint damage and renal complication
- Indications for starting urate lowering therapy: Any one of the following
  - Recurrent acute flares (≥ 2 flares in one year)
  - Presence of tophi
  - Chronic joint damage: Clinical or radiologic
  - Renal stones in patients with hyperuricemia
  - First attack in patients who need continuation of diuretics
- **Allopurinol** is the first line urate lowering therapy
  - **Dose in patient's normal kidney function**
    - ✓ Start after two weeks of flare
  - Starting dose: Allopurinol 100mg/day
    - ✓ Dose should be escalated every 2-4 weeks, until target uric acid level is achieved.
    - ✓ Increase by 100mg every month until target serum uric acid level is achieved to a maximum dose of 800mg/day.
    - ✓ Most patients require about 300mg/day or above.
    - ✓ Once target serum uric acid level is achieved: follow up can be done every 4-6 months
  - **Dose in patients with significantly impaired kidney function**
    - ✓ Starting dose
  - eGFR 5—15ml/min: 50 mg twice weekly
  - eGFR 16—39ml/min: 50 mg every 2 days
  - eGFR 31—45ml/min: 50 mg daily
    - ✓ Maximum dose for patients with eGFR<30m/min 300mg/day

Precautions with Allopurinol

Allopurinol is generally well tolerated; however, **severe cutaneous drug reactions** can rarely happen and **be fatal**.

Hence, all patients taking the drug need to be informed to **stop the drug immediately and seek medical attention**, if they notice **rash or have itching.**

- **Target serum uric acid level**
  - Non tophaceous Gout: < 6mg/dl
  - Tophaceous gout: < 5mg/dl
- **Prophylaxis** for flares during urate lowering therapy
  - During initiation and dose escalation of Allopurinol gout flares are common
  - Prevention of flares is needed during the first 06 months of Allopurinol therapy.
  - For patients with **normal kidney function**

First line

- ✓ Colchicine 0.5 to 1mg/day

Alternative (if cardiovascular risk is low)

- ✓ low dose NSAIDs with PPI (e.g. Diclofenac 50mg -75mg/day, Ibuprofen 200-400mg BID)

B) In situations when colchicine or NSAIDs are not tolerated/not available/ contraindicated: Prednisolone 5 to10mg/day

- ❖ For patients with **impaired kidney function**:

  First line

  - ✓ Prednisolone 5 to10mg/day

Non pharmacologic management of Gout

- Non- pharmacologic management is essential in all patients with gout. The non-pharmacologic management includes the following three elements:
  - ❖ Dietary management
  - ❖ Life style management and screening for cardiovascular risk factors
  - ❖ Education

1. Dietary management

- Dietary management alone is insufficient to control gout but it is an important adjunct.
- Excessive focus on dietary management without using effective urate-lowering therapy should be avoided.

Foods which need to be **restricted**	Remark
Meat	There is no difference among the red meat types (beef, lamb, goat meat or mutton)
Alcoholic drinks including beer	Red wine in moderation has the lowest risk
High sugar containing drinks and foods	

Foods should **encouraged** or not restricted	Remark
Milk and dairy products	Encourage
Fruits and vegetables	Encourage
Egg	Encourage
Bean, peas, chickpea	Safe and can be taken safely

2. **Life style management and cardiovascular risk screening**

- Weight reduction should be encouraged in overweight and obese individuals.
- All patients with gout should be screened for hypertension, diabetes, and dyslipidemia.

3. **Education**

- All patients with gout should be educated on flare management, the purpose and the lifelong nature of urate lowering therapy, adherence, dietary and life style management
- Educate patients and their families on the common misconceptions on the dietary management of gout.

3.11.1.2 Systemic lupus erythematosus (SLE) (lupus)

- SLE is a multi-system autoimmune disease with chronic, relapsing-remitting course and variable manifestations.
- Manifestations could range from a mild one to a life-threatening.
- The diagnosis of the disease could be challenging as it might have unpredictable course and mimic many other systemic diseases.
- SLE can affect any organ including the musculoskeletal, skin, hematologic, renal, neuropsychiatric, cardiovascular, and respiratory system.
- Not all manifestations appear simultaneously. Interval between the different manifestations could be months or years.
- Constitutional (especially fatigue), mucocutaneous and musculoskeletal symptoms tend to occur early.
- **Females are much more commonly affected than males (F:M ratio = 9:1).**

- The age of onset also ranges childhood to old age. The common age of onset is third to 3rd to 5th decade.
- Renal disease is the commonest organ/life threatening involvement.
- Lupus is associated with increased risk of thrombosis and accelerated atherosclerosis
- Pregnancy increases the risk of flare and should be avoided unless the lupus in remission for more than six months.

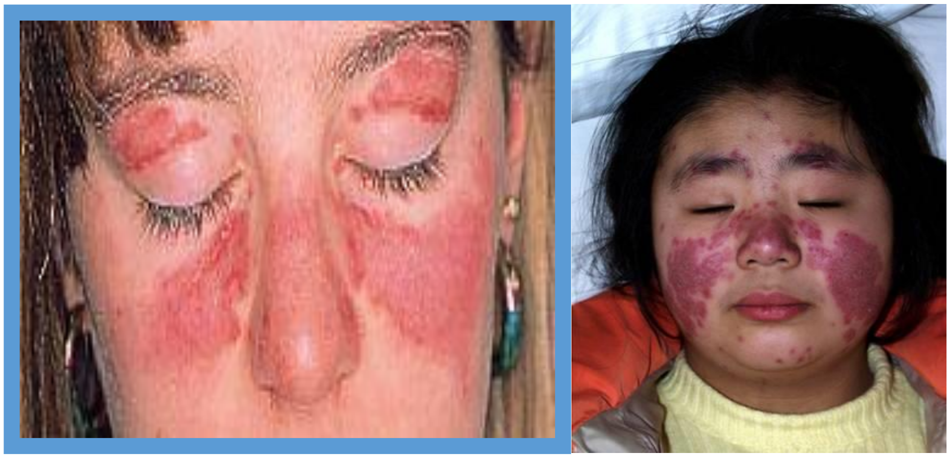
Clinical features

Symptoms

- Constitutional symptoms: Fatigue, fever, weight loss
- Mucocutaneous: Increased hair loss, photosensitivity, acute or subcutaneous/subacute and chronic skin lesions
- Musculoskeletal: Joint pain/swelling, morning stiffness, deformities can also happen
- Pulmonary: Cough, shortness of breath, pleuritic chest pain
- Cardiovascular: chest pain
- Renal: body swelling, decrement in urine amount, reddish urine, foaming of urine
- Neurologic: headache, seizures, decreased cognition, changes in mental status, weakness of extremities, features of painful peripheral neuropathy
- Psychiatric: behavioral changes

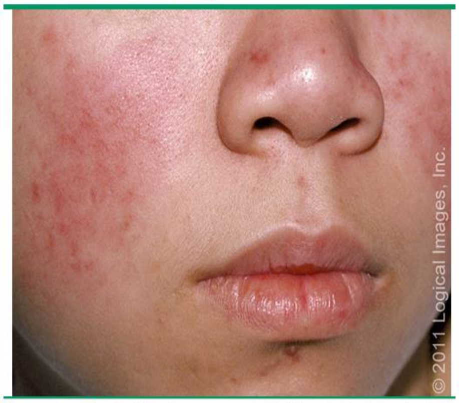
Signs

- Mucocutaneous: malar rash (butterfly shaped rash), maculopapular or bullous lesions, scaring discoid rash, painless oral ulcers, non-scaring alopecia
- Musculoskeletal: joint swelling, tenderness and decreased mobility
- Pulmonary: signs of pleural effusion, pleural friction rub, crackles
- Cardiovascular: signs of pericardial effusion, pericardial friction rub
- Renal: edematous state
- Neurologic: focal neurologic deficit, low score on mine mental test
- Psychiatric: behavioral changes



Picture; Malar rash (butterfly shaped rash)

Acute cutaneous lupus erythematosus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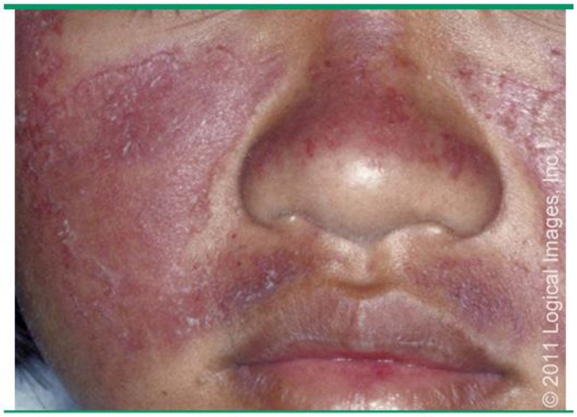
Malar erythema and subtle edema are present in this patient with systemic lupus erythematosus.

Acute cutaneous lupus erythematosus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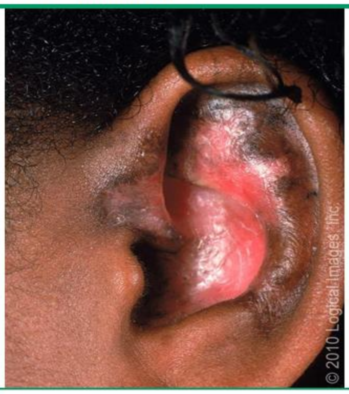
An erythematous, edematous eruption is present on the malar area. Note the sparing of the nasolabial folds.

Discoid lupus erythematosus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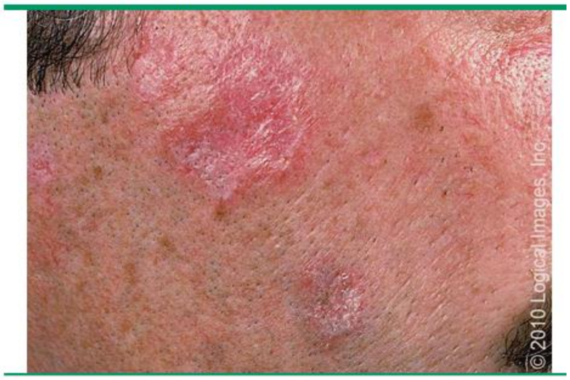
A well-defined, erythematous plaque with scale, pigmentary alteration, and scarring is present on this patient with discoid lupus erythematosus.

Discoid lupus erythematosus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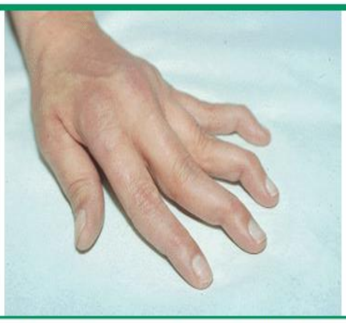
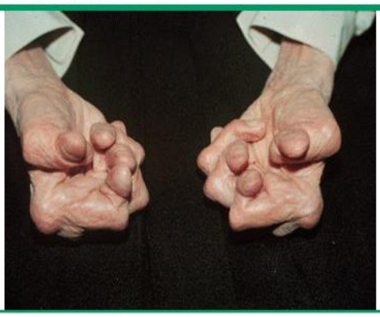
Well-defined, erythematous plaques with scale are present on the cheek of this patient with discoid lupus erythematosus.



Lupus arthritis

Patient with longstanding lupus has developed subluxation at the MCP joints and swan neck deformities of her fingers. These deformities are reducible (probably being due to lax tendons) and radiographs reveal no erosions or cysts, both of which differentiate these findings from those in rheumatoid arthritis.



Deforming lupus arthritis

Severe hand deformities in a 75-year-old woman with lupus for more than 20 years. Such hand abnormalities are very rare.

Investigation and diagnosis

Investigations

- Autoantibodies
  - ANA
  - Anti-dsDNA
  - Anti-Smith
  - Anti-phospholipid antibodies: Lupus anticoagulant, anti-cardiolipin, beta-2 glycoprotein
- Investigations for systemic involvement
  - CBC → anemia, thrombocytopenia, leukopenia
  - U/A → proteinuria, hematuria
  - 24hour urine protein >500mg
  - Creatinine and urea
  - CXR → pleural effusion, interstitial infiltrates
  - Echo
  - MRI and MRA

Diagnosis

- The diagnosis of SLE is based on a constellation of clinical laboratory and autoantibody tests.
- The presence of cutaneous, musculoskeletal symptoms associated with constitutional symptoms in young or middle aged women unless explained by another obvious diagnosis should suspected to be SLE
- A high index of suspicion is needed.
- Classification criteria

- The two widely used classification criteria for SLE clinical diagnosis are the 2012 SLICC and 2019 EULAR/ACR
- Both have good sensitivity and specificity (83.7% to 96.7%); hence, it is advised to use either of them for the purpose of diagnosis in patients with clinical features suggestive of SLE.

<table>
<tr><th colspan="2">Table: The 2012 SLICC criteria for SLE classification
Ref.: Arthritis Rheum 2012; 64:2677-2686.</th></tr>
<tr><td colspan="2">➢ Diagnosis requires fulfillment of at least **four criteria**, with at least one clinical criterion AND one immunologic criterion OR
➢ Lupus nephritis as the **sole clinical criterion** in the presence of ANA or anti-dsDNA antibodies</td></tr>
<tr><th>Clinical Criteria</th><th>Immunological Criteria</th></tr>
<tr><td>➢ Acute cutaneous lupus
➢ Chronic cutaneous lupus
➢ Oral ulcers: palate
➢ Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
➢ Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and thirty minutes or more of morning stiffness.
➢ Serositis
➢ Renal
➢ Neurologic
➢ Hemolytic anemia
➢ Leukopenia (< 4000/mm3 at least once)
➢ Thrombocytopenia (<100,000/mm3) at least once</td><td>➢ ANA above laboratory reference range
➢ Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory
➢ Anti-Sm
➢ Antiphospholipid antibody: any of the following
➢ Low complement
➢ Direct Coombs test in the absence of hemolytic anemia</td></tr>
</table>

Treatment

Non-pharmacologic treatment

- Exercise
- Minimization of sun exposure: hat, umbrella
- Stress management

Pharmacologic management

- **NSAIDS:** for arthralgia and mild arthritis
- **Corticosteroids:** For multiple indications

  - Pulse steroid: for acute life or organ threatening
    - Methylprednisolone 250 - 1000mg IV for 3 days
  - High dose steroid: for severe organ/life threatening for 4-8 weeks with tapering after that
    - prednisolone 0.5-1mg/kg/day or equivalent
  - Moderate steroid: prednisolone >10 to 0.5mg/kg/day or equivalent
  - Low dose steroid (maintenance): ≤ 10mg

- **Antimalarial:** all patients with SLE in the absence of contraindication
  - Chloroquine phosphate 250mg/day or 250mg PO 5 times per week
  - Baseline and annual ophthalmologic screening is needed, for possible retinopathy.
- **Other immunosuppressive**:
  - For life/organ threatening indication or as steroid sparing
  - They should be prescribed by specialists who have experience in using them
    - Azathioprine
    - Methotrexate
    - Mycophenolate Mofetil
    - Cyclophosphamide
- Patients with SLE with renal, neurologic involvement should be consulted for the specialist urgently.

3.11.1.3 Rheumatoid arthritis (RA) /ቁርጥማት/

- RA is a chronic systemic inflammatory disease mainly characterized by symmetrical polyarthritis of the small joins of hand and feet with progressive damage of joints.
- In addition to joints, it affects the lung (ILD, Pleurisy, PAH), blood (cytopenia and Felty's syndrome), skin (erythema nodosum and a variety of vasculitic lesions) and less commonly other organs.
- It more common in women than men.
- Although the onset can be at any age, the peak is 50-60 year in women and >70 year in men.

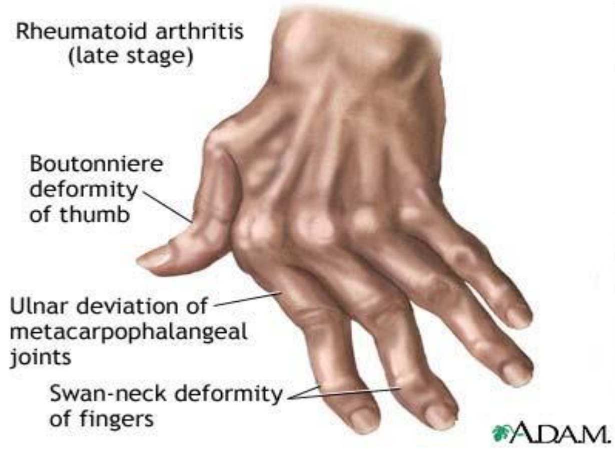
Clinical features

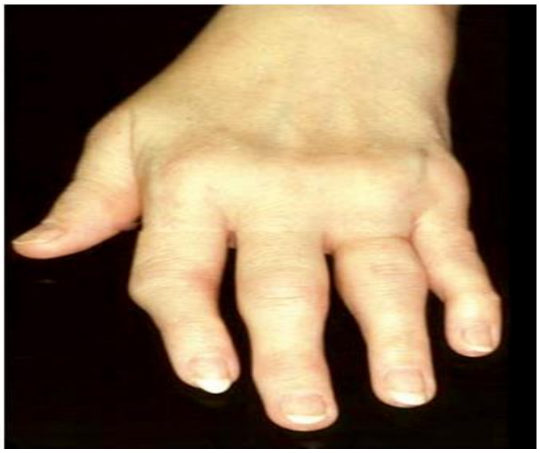
Symptoms

- **Joints symptoms**
  - The most typical symptomatic presentation of RA is that of a **symmetric polyarthritis** (defined as involving > 5 joints), involving small joints of the hands, wrists, and/or feet.
  - Joint pain
  - Joint swelling
  - Early Morning stiffness: usually lasts > 02 hours
  - Limitation of joint mobility (difficulty of using the joint)
- **Constitutional symptoms**
  - Fatigue
  - Generalized musculoskeletal pain
  - Weight loss
- **Symptoms from other organ-system involvement (extra-articular symptoms)**
  - Occasionally patients may also present with other organ involvements:
  - Cough, shortness of breath, chest pain: Lung involvement
  - Dryness of the eyes, red and/or painful eyes: Eye involvement
  - Swellings(nodules), red/dark lesions, ulcers on the skin : Skin/vascular involvement
  - Numbness or pain over the extremities: Peripheral nerve involvement

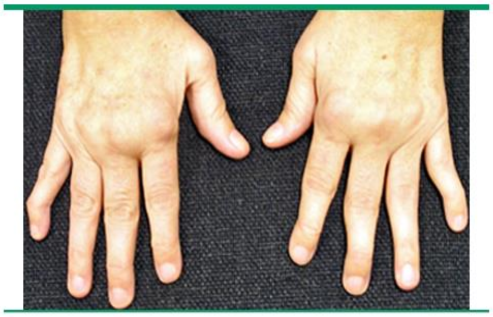
Signs

- **Joint**
  - Swelling (bogy swelling from effusion or subtle swelling from thickening)
  - Tenderness
  - Deformities (**swan neck deformity of fingers**, ulnar deviation of MCP joints, Boutonniere deformity of thumb…)
- **Other organ-systems (extra-articular signs):**
  - Depending on the systems involved e.g. subcutaneous nodules, enlarged lymph nodes, signs of pleural/pericardial effusion, splenomegaly


Rheumatoid arthritis (late stage)
Boutonniere deformity of thumb
Ulnar deviation of metacarpophalangeal joints
Swan-neck deformity of fingers
ADAM.

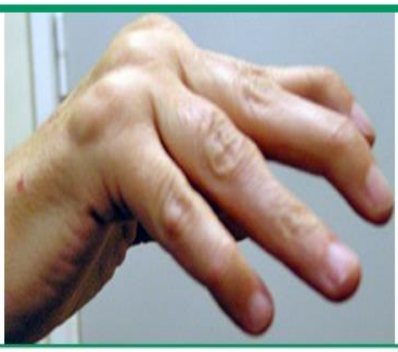


Synovial thickening of the metacarpophalangeal joint



Bilateral swelling of the MCP joints is evident in this patient with rheumatoid arthritis. Note also the mild swan neck deformities present in several fingers, particularly the left middle and fifth fingers.

Swelling of the metacarpophalangeal joints of the right hand in rheumatoid arthritis



Swelling of the MCP joints, moderate MCP flexion, and swan neck deformities are evident in this patient with rheumatoid arthritis.

Investigations and diagnosis

- RA should be strongly suspected in any patient who present with multiple joint pain, swelling and morning stiffness for few weeks.
- Hand, wrist, and foot joints are the most commonly involved; however, any joint can be involved.
- Distal interphalangeal (DIP) joints are usually spared in RA.
- The spine (the back), apart from the atlantoaxial joint, is not directly involved by inflammation but may be affected by osteoporosis and mechanical imbalance due to involvement of the weight bearing joints.
- There is no single test, imaging finding or clinical finding which is diagnostic of RA. A strong clinical suspicion is needed in any patient when with polyarthritis for few weeks.
- The classification criteria for RA is designed for the purposes in researches, but it is a good clinical guide to make a diagnosis with a reasonable sensitivity
- **Rheumatoid factors (RFs)**

- ✓ Sensitivity: About 70% of patients are positive at diagnosis.
- ✓ False positivity: other CTD like SLE and some infectious diseases like malaria and hepatitis C
- ✓ False negativity: Nearly one third of patients with RA are negative RFs results

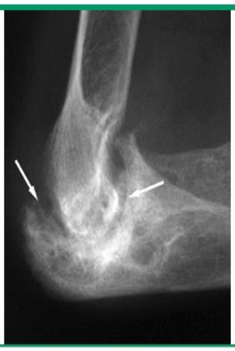
➢ **Anti-CCP (Anticyclic-citrullinated peptide) antibody test**

- ✓ Sensitivity: Similar to rheumatoid factors
- ✓ Specificity: > 95%.

➢ **Other investigations**

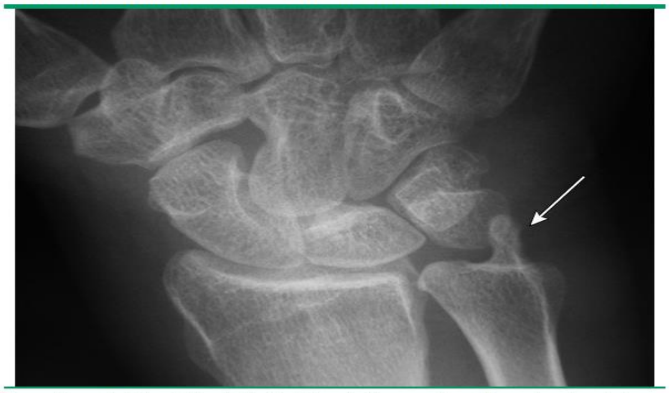
- ✓ ESR or CRP: Moderately increased ESR (usually not >50ml/min) or CRP. ESR and CRP may be normal in about one-third of patients.
- ✓ CBC: Norma WBC, mild anemia (due to chronic inflammation), or thrombocytosis (due to chronic inflammation)
- ✓ Imaging (X-ray): in early disease X-ray is usually normal, as the disease advances X-ray shows decreased bone density, bone erosion, joint space narrowing, and deformities.

Rheumatoid arthritis of the elbow



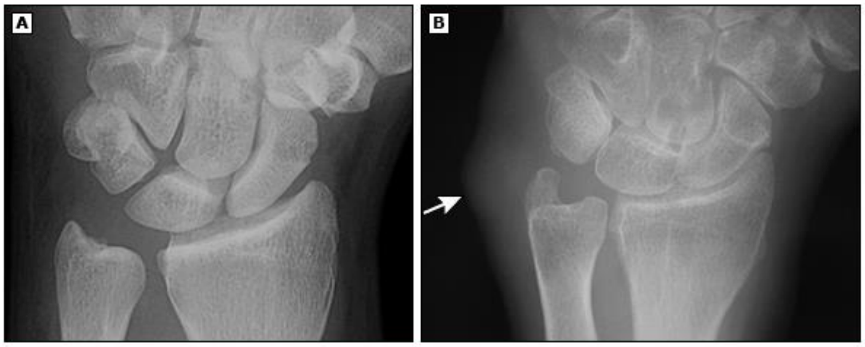
Lateral view of the elbow in a patient with rheumatoid arthritis (RA) reveals soft tissue swelling and osteopenia with destruction of the elbow joint (arrows). There are also secondary proliferative bony changes, which have arisen due to joint space destruction.

Plain radiograph of ulnar styloid erosion in rheumatoid arthritis



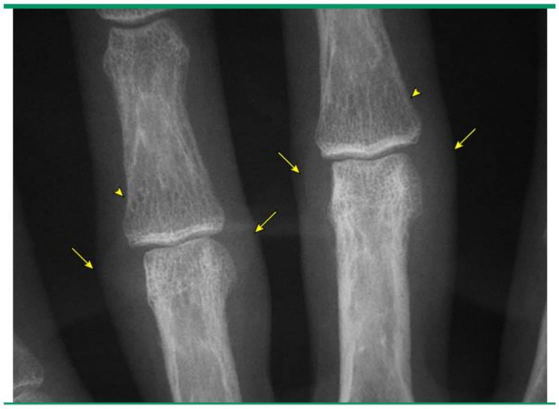
The radiograph of the right wrist in the AP projection reveals a deformed and eroded ulnar styloid process (arrow) in this patient who has rheumatoid arthritis. No other remarkable changes are present.

Plain radiograph of osteopenia of the wrist in rheumatoid arthritis



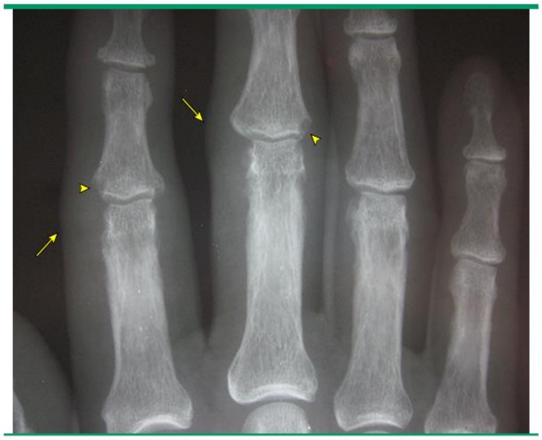
The normal radiograph of the left wrist in the AP projection (A) is compared with the left wrist of a patient with rheumatoid arthritis (B). The subtle diffuse osteopenia of the carpal bones is typified by an overall decrease in the density of the bones and by a relative paucity of trabecular markings. Less subtle is the prominent soft tissue nodule overlying the styloid process (arrow).

Soft tissue swelling and periarticular osteopenia of proximal interphalangeal joints in rheumatoid arthritis



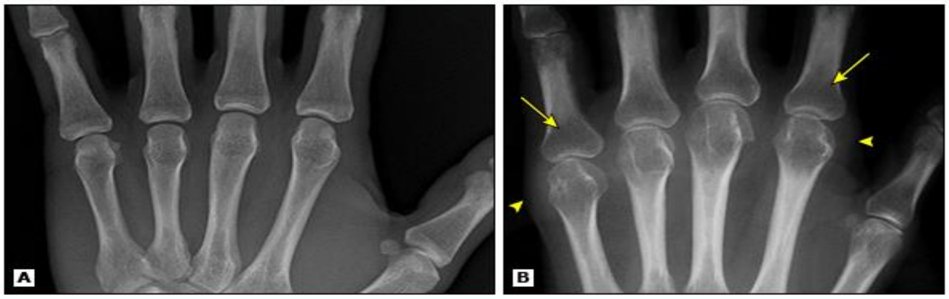
The plain radiographs of the hand are magnified at the proximal interphalangeal joints of the third and fourth fingers showing soft tissue swelling (arrows) and periarticular osteopenia (arrowheads).

Plain radiograph of rheumatoid arthritis proximal interphalangeal joint erosions



The plain x-ray of the right hand magnified at the proximal interphalangeal joints shows soft tissue swelling (arrows) and mild erosive changes (arrowheads).

Plain radiograph of osteopenia of metacarpophalangeal joints in rheumatoid arthritis



The plain radiograph of the left hand in the AP projection shows a normal patient (A) and a patient with radiologically mild rheumatoid arthritis (B). The patient with rheumatoid arthritis demonstrates osteopenia around the metacarpophalangeal joints (arrows) and mild soft tissue swelling (arrowheads).

ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis

- These criteria should be restricted to persons with at least one clinically detectable swollen joint in the absence of a more likely diagnosis
- A score **of ≥6 points** is classified as **definite RA.** In each domain, consider only the category with most points.

A. **Joint involvement and distribution (0-5 points)**

- Any swollen or tender joint on physical examination
- Large joints: Shoulders, elbows, hips, knees, and ankles
- Small joints: Metacarpophalangeal, proximal interphalangeal, second through fifth metatarsophalangeal, thumb interphalangeal, and wrists
    - ✓ 1 large joint → 0 point
    - ✓ 2—10 large joints → 1 point
    - ✓ 1—3 small joints → 2 points
    - ✓ 4—10 small joints → 3 points
    - ✓ > 10 joints (and at least 1 small joint) → 5 poin

B. **Serology (0-3 points)**

- ✓ Low-positive results are > 1 to 3 times the upper limit of normal of the assay used.
- ✓ High-positive results are > 3 times the upper limit of normal of the assay used
- ✓ Negative RF and negative ACCP → 0 point
- ✓ Low-positive RF or low-positive ACCP → 2 points
- ✓ High-positive RF or high-positive ACCP → 3 points

C. **Acute-phase reactants (0-1 point)**

- ✓ Normal CRP and normal ESR → 0 points
- ✓ Abnormal CRP or abnormal ESR →1 point

D. **Duration of symptoms (0-1 point)**

- Patient's self-report on the maximum duration of symptoms of any joint clinically involved at the time of assessment
    - ✓ < 6 wk → 0 point
    - ✓ ≥6 wk →1 point

Treatment

Pharmacologic treatment

- **Disease-modifying antirheumatic drugs (DMARDS)**
  - All patients with RA should be started with DMARDS without any delay
  - If DMARDs are not available or you don't have the experience of using them, the patient should be referred.

1) First line DMARD: Methotrexate (MTX) 7.5 - 25mg/once per week

- **Investigation before initiation of MTX**: CBC, liver enzymes, screening HBV and HCV, BUN and Creatinine, Chest X-ray.
- **Starting dose:** 7.5mg - 10mg per week, PO or Sc
- The MTX dose needs to be escalated by 2.5mg-5mg, at intervals no more frequent than every month until disease activity is well controlled or maximum tolerated dose is achieved.
- **Maximum dose:** 25mg/week
- All patients on MTX should be given **Folic acid** to prevent the hematologic and other side effects.
  - ✓ Folic acid 1mg tab, po/day or 5mg tab, po/2-3 times per week
- **Major adverse effects:** Liver toxicity, Bone marrow suppression (pancytopenia), lung toxicity and increased susceptibility to infection
- **Monitoring:** All patients need to have CBC and LFT monthly for the first 3 months, then every 03 months.
- **Contraindications to MTX:**
  - ✓ Pregnancy
  - ✓ CKD / Significant impairment in kidney function (eGFR<30ml/min),
  - ✓ CLD
  - ✓ Active/uncontrolled infection.

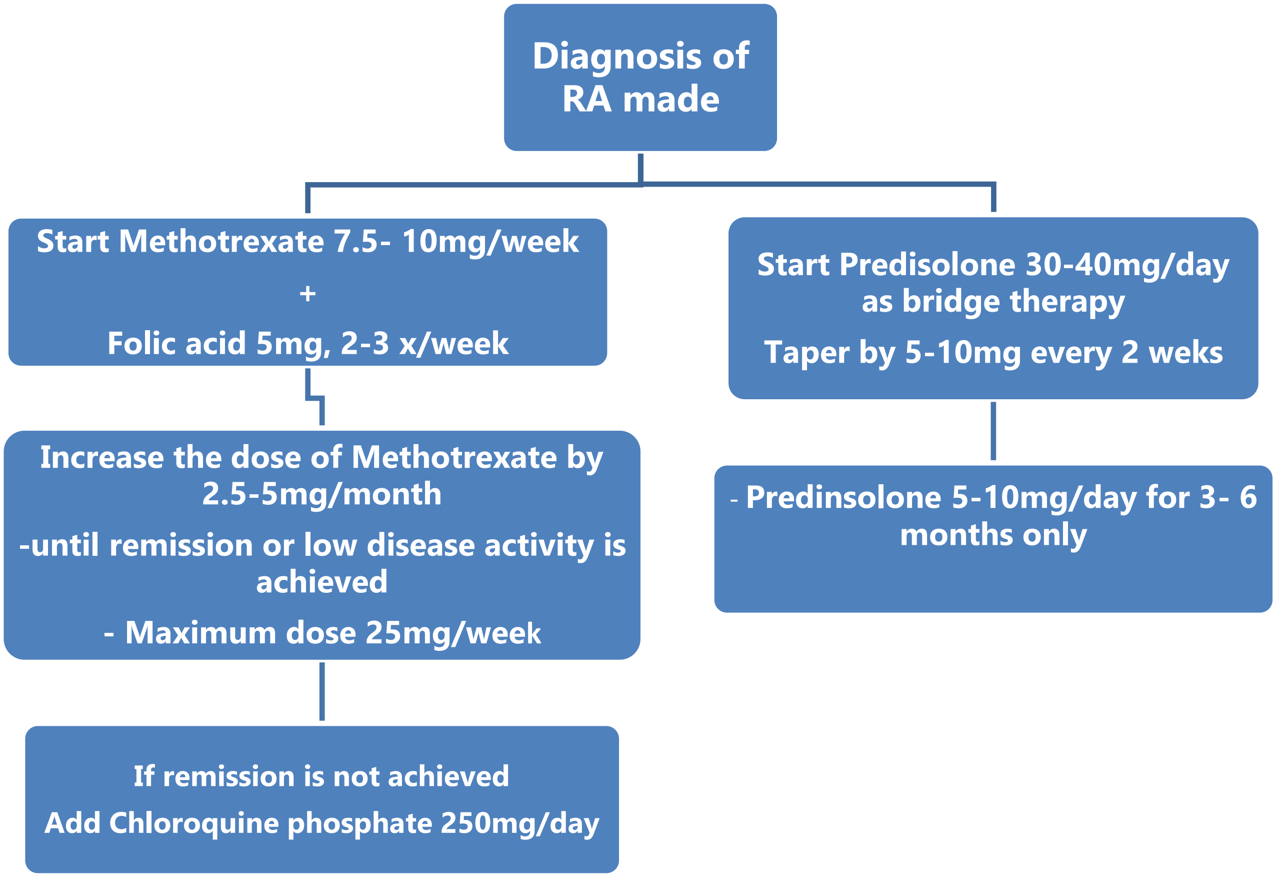
2) Additional or alternative DMARDS

- **Chloroquine: Chloroquine phosphate 250mg/day**
  - ✓ **As additional agent:** Add Chloroquine in patients who are having poor disease control while taking maximally tolerated dose or >15mg of MTX/week.
  - ✓ **As an alternative to MTX:** In patients for whom MTX is contraindicated or have mild disease Chloroquine can be used as an alternative.
  - ✓ **Dosing in adults:** Chloroquine phosphate 250mg tab (equivalent to chloroquine base 150mg), 01 tablet 5 times per week
- **Disease activity not well controlled by a combination of maximum/ maximally tolerated dose Methotrexate and chloroquine:**

  - ✓ Add low dose steroid (<10mg/day) as part of the DMARD and Consult specialist
- ➢ **Relieving acute inflammatory pain**
  First line: NSAIDS or short course corticosteroids
- ➢ NSAID options
  - ✓ **Ibuprofen,** 400-800mg, P.O, TID with meals.
  - ✓ **Diclofenac,** 150mg/day, P.O, in 2-4 divided doses. Rectal suppository 100mg/day
  - ✓ **Indomethacin,** 25-50mg P.O.TID; maximum dose: 200mg/day. Rectal suppository, insert 100mg, BID or once.
  - ✓ **Meloxicam,** 7.5 - 15mg/day. Maximum dose 15mg/day
  - ✓ **Piroxicam,** 10-20mg/day. Maximum dose 20mg/day
- ➢ Precautions with NSAIDS
  - ✓ Avoid NSAIDS in patients with impaired kidney function
  - ✓ Offer PPIs for those at high risk of NSAIDs associated peptic ulcer bleeding: patients with history of peptic ulcer symptoms, on Aspirin/anticoagulant /steroid

3) Corticosteroids: Indications

- ➢ As a bridge to DMARDS at diagnosis
  - ✓ Prednisolone
    - ▪ Starting dose: 20mg/day. Do not exceed 30mg/day.
    - ▪ Tapering: taper by 5-10mg every 2 weeks, keep it <10mg/day for 3-6 months until DMARDs take over.
  - ✓ Flare management
    - ▪ Prednisolone 15 -20mg/day taper to baseline dose or stop in 2 weeks
  - ✓ Chronic therapy
    - ▪ Corticosteroids are not generally regarded as DMARDS
    - ▪ Long term therapy is not recommended
    - ▪ In some patients where disease activity is poorly controlled while a combination maximum/maximum tolerated dose DMARDs low dose steroid may be needed
    - ▪ Prednisolone 5-10mg/day achieved


Diagnosis of RA made
Start Methotrexate 7.5- 10mg/week
+
Folic acid 5mg, 2-3 x/week
Start Predisolone 30-40mg/day as bridge therapy
Taper by 5-10mg every 2 weks
Increase the dose of Methotrexate by 2.5-5mg/month
-until remission or low disease activity is achieved
- Maximum dose 25mg/week
- Predinsolone 5-10mg/day for 3- 6 months only
If remission is not achieved
Add Chloroquine phosphate 250mg/day

3.11.1.4 Osteoarthritis (የአጥንት እና አንጓ ብግነት)

- Osteoarthritis (OA) is a joint disease which results from an active pathology involving the whole joint structure including cartilage damage, low grade joint inflammation, bone remodeling, and osteophyte formation.
- It was previously thought that OA is a degenerative disease; however, it is now understood that it is the result of active biochemical and cellular pathologic process.
- Joint pain and progressive loss of joint function result from the pathologic process.
- **The knee, hip and hand joints are the most commonly affected sites.**
- OA is considered to be the leading cause of join related disability in old adults.

Risk factors for OA

- ✓ Old age
- ✓ Overweight/obesity
- ✓ Female sex

  - ✓ Occupation
  - ✓ Injury/trauma.

Clinical features

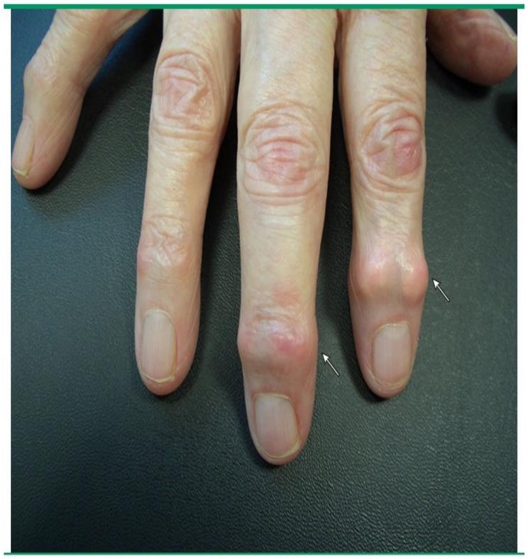
Symptoms

- ➢ Joint pain
  - ✓ Pain in OA is generally activity related and relived by rest. It is more intense at the start of activity.
  - ✓ It is worse in the afternoon and evening.
- ➢ Joint stiffness
  - ✓ The morning stiffness in OA is shorter (<30 minutes) compared to rheumatoid arthritis and other inflammatory arthritis.
- ➢ Symptoms of “crepitus”
  - ✓ Clicking, grinding or popping feelings
- ➢ Instability of joint:
  - ✓ Buckling or giving away feeling, lacking the confidence to use weight bearing joints
- ➢ Limitation of movement
- ➢ Deformity

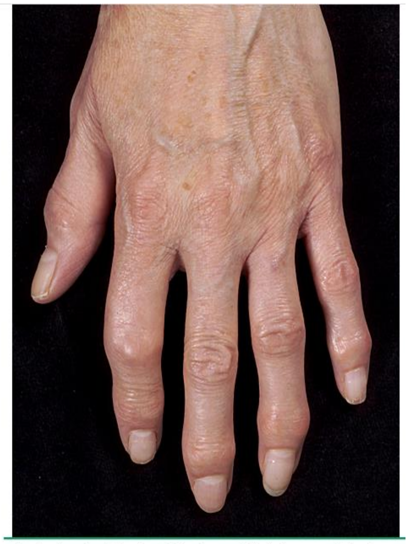
Signs

- ➢ **Distribution of joint involvement:**
  - ✓ Single joint OA: knees, hips, thumb, interphalangeal joints, cervical or lumbar spine
  - ✓ Generalized (Polyarticular) OA
    - More than two joint regions are involved.
    - Symptoms usually starts in the hands around middle age and subsequently affect the knees and other joints over several years
    - The main clinical sign is the presence of multiple **Heberden’s nodes** (hard/bony swelling in the DIP joints) or **Bouchard’s nodules** (hard/bony swellings in PIP joints)

Heberden's nodes



Heberden's nodes, appearing as discrete postero-lateral swellings (index finger) or as a dorsal bar (middle finger) over the DIP joints.



Heberden's nodes (thumb, middle, ring, and little finger DIP joints), Bouchard's nodes (index finger PIP joint), and lateral radial/ulnar deviation (index PIP joint, ring DIP joint) in the left hand of a person with nodal OA.

Investigations and diagnosis

- The diagnosis of osteoarthritis is clinical
- The presence of following three makes the diagnosis of OA highly likely:
  - ✓ Age ≥45 years
  - ✓ Joint pain in only one or few joints
  - ✓ Morning stiffness duration ≤ 30 minutes
- The presence of other clinical features e.g. Heberden's node, joint instability and crepitus makes the diagnosis of OA more certain.
- x-ray of the involved joint → support the diagnosis
- ESR or CRP: Generally normal in patients with OA.
- Investigations to exclude other differential diagnoses
  - ✓ Psoriatic Arthritis has to be ruled out in polyarticular OA
  - ✓ Rheumatoid factor/anti-CCP antibody if rheumatoid arthritis is suspected
  - ✓ Joint fluid aspiration may be needed

Treatment

Pharmacologic treatment

- **Pain management:**

First line

- ✓ NSAID's are first line:
  - Topical NSAIDS: For knee and other joints as well OA

- Systemic NSAIDS (oral or rectal suppository): For all types of OA including
  - For patients with high risk for GI bleeding use with PPI
  - NSAIDS are contraindicated in patients with history of upper GI bleeding and CKD

Second line → If NSAIDS are contraindicated or ineffective

- ✓ **Duloxetine:** Initial dose 30mg/day, increase t0 60mg/day after at least one week. Maximum dose 120mg/day
- ✓ **Acetaminophen (Paracetamol):** 1g TID to QID, Max;4g/day.
- ✓ **Tramadol:** Dose for immediate release: 50mg/day and increase to 50mg BID. Gradually increase to 50mg QID. Max; 300mg/day

Drugs which **are not recommended** for the management of OA

- Non-tramadol opioids
- Systemic steroids
- Colchicine
- Bisphosphonates
- Methotrexate

Intra-articular steroids can be used for Pain management in knee or hip (for hip it should only be image guided) which can be given by specialist who have experience.

Non-pharmacologic management

- Exercise:
  - ✓ Both aerobic (e.g. walking) and local muscle strengthening are useful
  - ✓ Tai Chi (a form of Chinese martial art practice along with meditation) and Yoga
- Weight loss: For overweight individuals with knee or hip OA
- Patient education: including self-management
- Cane or walking stick /for knee or hip OA/, braces/ tibiofemoral knee braces for knee OA / and orthosis / Hand orthosis for first carpometacarpal joint
- Surgical treatment
  - ✓ Total joint replacement hip or knee) can be considered in patients with end-stage OA (i.e. severe persistent symptoms and marked

functional impairment). Patients should be referred to specialized hospitals or centers.

The following surgical interventions are not recommended

- Arthroscopic debridement
- Abrasion arthroplasty (involving burring and drilling of sclerotic bone)
- Synovectomy

3.11.2 MSS infections

3.11.2.1 Pyogenic Osteomyelitis

- Pyogenic Osteomyelitis is an acute infection of the bone and its structures caused by bacteria.
- Osteomyelitis occurs as a result of hematogenous spread, contiguous spread from adjacent soft tissues or direct infection from trauma or surgery.

Aetiology

- Hematogenous osteomyelitis is usually monomicrobial, while osteomyelitis due to contiguous spread or direct inoculation is usually polymicrobial.
- **S. aureus is the most common** causative organism.
- Coagulase- negative staphylococci and aerobic gram-negative bacilli are also common causes.
- Streptococci, enterococci and anaerobes are also implicated.

Clinical features

- Gradual onset varying from few days to weeks of local bone pain, swelling, low grade fever, malaise and weight loss.

Investigations

- Usually Clinical Dx
- CBC
- ESR & CRP
- X-ray of the affected bone
- Culture of pus/sequester (if debridement is done)

Treatment

Non pharmacologic

- Rest/immobilization
- Surgical debridement (Drainage by surgeon/orthopedic surgeon)
- **N.B.** Osteomyelitis frequently requires both surgical therapy for debridement of necrotic material together with antimicrobial therapy for eradication of infection. The debrided necrotic material should be sent for culture.

Pharmacologic

- **Empiric antibiotic**
  - ✓ Empiric treatment with activity against S. aureus (especially MRSA) and gram-negative organisms is required.

First line

- ✓ **Vancomycin**, 30mg/kg/day, IV, BID (initially 20 mg/kg loading dose, not to exceed 2 g/dose)

  PLUS
- ✓ **Ciprofloxacin**, 750mg, P.O., BID OR
- ✓ Ceftriaxone 2 g IV daily

Alternative

- ✓ **Cloxacillin**, 2gm, I.V. QID PLUS
- ✓ **Ciprofloxacin**, 750mg, P.O., BID

Once susceptibility results were available, specific drugs should be used.

Duration of therapy

- ✓ Duration of antibiotics is for **at least 6 weeks**
- ✓ For patients with **residual infected bone** that is not amenable to complete removal should be treated **at least for 6 weeks duration after the last debridement** (optimal duration is uncertain).
- ✓ For patients who undergo **amputation or complete removal of all involved bone** warrant a **5 days** course of antibiotic therapy **after complete debridement.** If there is evidence of **soft tissue infection** at the operative side pathogen-directed **10 to 14 days parenteral or highly bioavailable oral agent** can be used.
- ✓ In the presence of **orthopedic hardware**, **6 weeks parenteral therapy following debridement** is used. Thereafter, long-term antibiotic suppression with an oral agent, guided by antimicrobial susceptibility data is recommended. Suppressive therapy is warranted only for individuals with retained hardware and/or necrotic bone not amenable to complete debridement. Oral suppression antibiotics should be continued at least until fractures are united (demonstrated radiographically).

N.B. Further treatment is guided by culture sensitivity tests

For pain and fever

- ✓ Analgesic/antipyretic e.g. **Paracetamol,** 500mg -1g P.O. PRN (4- 6 times daily) can be given.

Monitoring For patients on parenteral antimicrobials:

- ✓ **Weekly CBC and chemistries** should be performed.

- ✓ In addition, **ESR & CRP** should be obtained at the beginning and end of parenteral treatment (at any time in between if clinical suspicion for treatment failure) and at the time of transition to oral suppressive therapy (if used).
- ✓ If inflammatory markers persistently elevated two weeks after completion of antibiotic therapy (in the absence of alternative explanation) possibility of persistent osteomyelitis be considered.
- ✓ If a patient has associated symptoms, evaluate completeness of the debridement, review microbiologic diagnosis and susceptibility data and thus may warrant repeated debridement and additional antimicrobial therapy.
- ✓ If no clinical signs consistent with persistent infection, clinical observation is reasonable.
- ✓ For patients on **oral suppressive antibiotic therapy**:
- ✓ **CBC, creatinine, and ALT at 2, 4, 8, and 12 weeks and then every 6 to 12 months thereafter.**

3.11.2.2 Septic Arthritis

- ➢ The term septic arthritis refers to bacterial infection of a joint.
- ➢ Septic arthritis is dangerous and destructive to the joint.
- ➢ It may occur secondary to hematogenous spread (80-90%), contiguous spread (10-15%), and direct penetration of microorganisms secondary to trauma, surgery or injection.
- ➢ **Old age, DM, skin infection, alcoholism, intra-articular injections are some of the common risk factors.**
- ➢ **S. aureus is the most common cause.**
- ➢ Streptococci and other gram positive are also frequent causes.
- ➢ Gram-negative bacilli are found as causes in specific situations such as trauma, immunosuppression and very elderly.

Clinical features

- ➢ Septic arthritis presents acutely and mostly with **a single swollen and painful joint.**

Investigations

- ➢ CBC
- ➢ ESR/CRP
- ➢ Synovial fluid analysis → cell count (WBC count) with differentials, Gram stain, AFB, culture (two sets), and assessment for crystals.
- ➢ X-ray of the affected joint

Diagnosis

- ➢ Septic arthritis should be suspected in patients with acute onset of at least one swollen, painful joint.

- Septic arthritis diagnosis should be established based on synovial fluid analysis and culture.
- Septic arthritis could be definitively established if positive synovial fluid gram stain and/or culture are obtained.
- In patients with purulent synovial fluid (leukocyte count of 50,000 to 150,000 cells/µl, mostly neutrophils) but negative synovial fluid cultures, a presumptive diagnosis septic arthritis may be made.
- If synovial fluid culture is negative and no purulent fluid, alternative diagnosis should be considered.

Treatment

- In general, management of acute bacterial arthritis involves joint drainage (since this condition represents a closed abscess) and antimicrobial therapy.

Non pharmacologic

- Aspiration/drainage: needle aspiration, arthroscopy, or arthrotomy (open surgical drainage)
- Splintage, but early immobilization if joints are mobile.
- The joint must be splinted with a POP slab or skin traction to relieve pain and prevent contractures

Pharmacologic → Empiric antibiotics

- Prior to antibiotics administration, sent synovial fluid analysis

First line

- ✓ **Vancomycin**, 30mg/kg/day, IV, BID, not to exceed 2g/day for 4-6 weeks PLUS
- ✓ **Ceftriaxone**, 2gm, I.V, daily for 4-6 weeks or
- ✓ cefotaxime 2 g IV TID

Alternatives

- ✓ **Cloxacillin,** 2g, IV, QID for 4-6 weeks plus
- ✓ **Ceftriaxone** 2gm, IV, daily or
- ✓ cefotaxime 2 g IV TID

- NB: For suspected septic arthritis (in the above regimens) due to **MRSA Vancomycin** is a suitable. Alternatives include clindamycin, Cotrimoxazole, doxycycline, linezolid, and rifampin in combination with either ciprofloxacin or fusidic acid.
- For suspected septic arthritis due to **MSSA** suitable choices include **Cloxacillin**, dicloxacillin (500 mg, PO, QID), flucloxacillin (500 mg, PO, QID), or cephalexin (500 mg, PO, QID).
- Patients who are allergic to penicillin can be treated with clindamycin (600 mg, PO, TID).

Synovial fluid analysis (gram stain) and Empiric therapy choice (until susceptibility results are available):

- If synovial fluid gram stain shows **gram positive cocci →** use **vancomycin** with the above dose as first line and Cloxacillin as alternative.
- If synovial fluid grams stain shows **gram negative bacilli -**use third-generation cephalosporin (use **ceftriaxone** with the above dose) as first line.
- If the initial Gram stain of synovial fluid is n**egative but synovial fluid cell count is consistent with septic arthritis** (purulent fluid of 50,000 to 150,000 cells, mostly neutrophils), the approach depends on individual clinical circumstances.
    - ✓ For immunocompetent patients without confounding factors (such as trauma), use vancomycin.
    - ✓ For immunocompetent patients with traumatic bacterial arthritis, use vancomycin plus a third-generation cephalosporin.
    - ✓ For immunocompromised patients and injection drug users, use vancomycin plus a third-generation cephalosporin (ceftriaxone).
    - ✓ Ceftazidime (2 g IV TID) or cefepime (2 g IV TID to QID) should be used in place of ceftriaxone if there is a high risk for Pseudomonas infection.
    - ✓ Consequently, antibiotic therapy should be adjusted to culture and susceptibility data once available.

Duration of therapy

- Duration of antibiotic treatment is 4-6 weeks (optimal duration is uncertain).
- At least the first 2 weeks of antibiotics should be through IV route.
- For susceptible pathogens durations may be shorter than indicated (e.g. fluoroquinolone susceptible pathogens can be treated for 5 to 7 days of parenteral, followed by 14 to 21 days of oral fluoroquinolone with careful monitoring of the compliance and response).
- For staphylococcus bacteremia (in the absence of endocarditis) 4 weeks parenteral treatment is recommended.
- If no staphylococcus bacteremia 1 to 2 weeks oral therapy can be used after 1 to 2 weeks of parenteral therapy.
- For patients with septic arthritis with endocarditis, treat for duration required for endocarditis.
- Patients with septic arthritis and contiguous osteomyelitis require a long (4-6 weeks) course of antibiotics.

3.12 Miscellaneous

3.12.1 Anaemia (የደም ማነስ)

- Anemia is not a disease by itself but a manifestation of different disease entities (causes)

- Anemia is functionally defined as reduction in RBC mass, accompanied by a decrease in oxygen carrying capacity.
- Laboratory wise anemia is defined as a reduction in one or more of the three RBC measurements in the CBC: Hgb, hematocrit (HCT), or RBC count. For practical purposes, hemoglobin or hematocrit are commonly used.
- **WHO criteria for diagnosing anemia in men and women are hemoglobin values <13 and <12 g/dl, respectively.**
- Anemia is not a single disease entity; it is rather a manifestation of several pathologies.

Classification of anemia

- Designed for systematic approach of different causes of anemia
- There are two approaches of classification

I. Kinetic approach→ Based on the mechanisms responsible for the anemia

II. Morphologic approach → Based on the size of RBCs and the reticulocyte response

1. Kinetic approach

A) Anaemia due to decreased RBC production
  - ✓ Also known as ineffective erythropoiesis
  - ✓ Causes include
    - Lack of nutrients- iron, folate, or B12
    - Bone marrow disorders- aplastic anemia, MDS, tumour infiltration
    - Bone marrow suppression- drugs, irradiation
    - Anemia of chronic disease/inflammation

B) Anemia due to increased RBC destruction
  - ✓ Haemolytic anemias

C) Anemia due to blood loss
  - ✓ Obvious or occult bleeding

Morphologic approach

- **Size → as measured by mean corpuscular volume (MCV)**
  - ✓ The normal RBC has a volume (MCV) of 80-100 femtoliters (fL), equal to that of the nucleus of a small lymphocyte

- ✓ RBCs larger than the nucleus of a small lymphocyte on a peripheral smear are considered macrocytic, while those that appear smaller are considered microcytic

- ➢ **Chromicity**
  - ✓ **Normochromic →** MCH = 27-33 or central pallor of RBCS < 1/3rd of the size of RBC
  - ✓ **Hypochromic →** MCH <27 or central pallor >1/3rd of the size of RBC

a. **Macrocytic normochromic anemia**
  - ✓ MCV >100fL
  - ✓ Causes include
    - Folate deficiency
    - Vit.B12 (Cobalamin) deficiency
    - Any condition causing marked reticulocytosis
    - Alcohol abuse
    - Hypothyroidism
    - Drugs- zidovudine, methotrexate, and hydroxyurea
  - ✓ Megaloblastic anemia
    - Due to folate and cobalamin deficiency
    - Characterized by hypersegmented neutrophils

b. **Microcytic hypochromic anemia**
  - ✓ MCV<80 fl
  - ✓ Causes include;
    - Iron deficiency anaemia
    - Lead poisoning
    - Sideroblastic anemia
    - Thalassemia
    - Anemia of chronic illness (30% of the cases)

c. **Normocytic normochromic anemia**
  - ✓ MCV 80-100 fl
  - ✓ Causes include;
    - Anemia of chronic illness (70% of the cases)
    - CKD
    - Early iron deficiency anemia
    - Acute blood loss

Table; Classification of anemia based on hemoglobin level or severity; WHO 2015

Population		Hemoglobin level (in g/dl)			
		Non-anemia (Normal)	Anemia		
			Mild	Moderate	Severe
Children 6-59 months of age		≥ 11	10-10.9	7-9.9	<7
Children 5-11 years of age		≥ 11.5	11-11.4	**8-10.9**	**< 8**
Children 12-14 years of age		≥ 12	11-11.9		
Men ≥ 15 years of age		13.3 - 16.2	**11-12.9**		
women ≥ 15 years of age	**Non pregnant**	12.0 - 15.8	**11-11.9**		
	Pregnant	≥ 11	**10-10.9**	**7-9.9**	**< 7**

Clinical features

Symptoms

- Fatigue, dyspnea, palpitation, syncope
- Headache, lightheadedness, tinnitus, vertigo, difficulty of concentration
- Anorexia, nausea, indigestion
- Symptoms s of the underlying disease e.g. melena in GI bleeding, heavy menstrual bleeding, generalized body swelling in CKD,

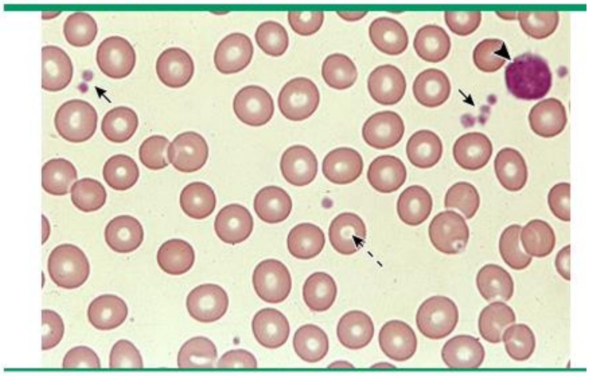
Signs

- Pallor, tachycardia, wide pulse pressure /ejection systolic murmur.
- Signs of Heart Failure (raised JVP, S3, hepatomegaly, edema)
- Signs of the underlying disease-causing anemia: lymphadenopathy, splenomegaly, angular chelitis, tumors (abdominal/ pelvic mass) etc.

Investigation and diagnosis

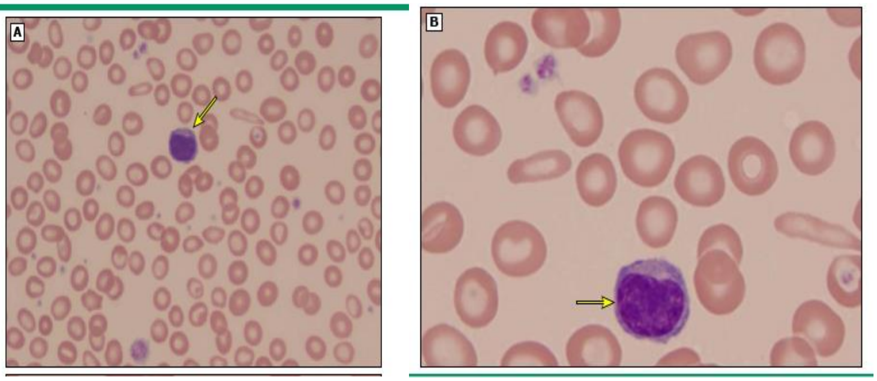
1) CBC with RBC indices
2) Peripheral blood smear
3) Reticulocyte count and index

Normal peripheral blood smear



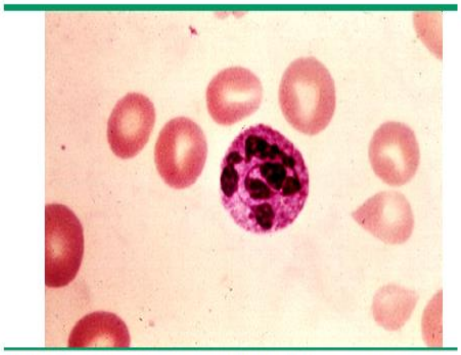
Picture; High-power view of a normal peripheral blood smear. Several platelets (arrows) and a normal lymphocyte (arrowhead) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Peripheral blood smear in iron deficiency anemia showing microcytic, hypochromic red blood cells



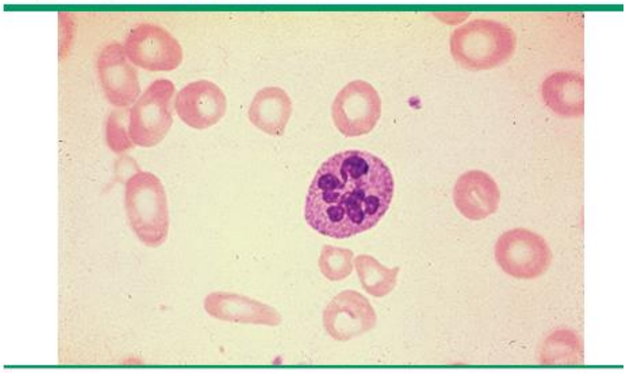
Picture; peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for size comparison (arrow). Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

Hypersegmented neutrophil in megaloblastic anemia

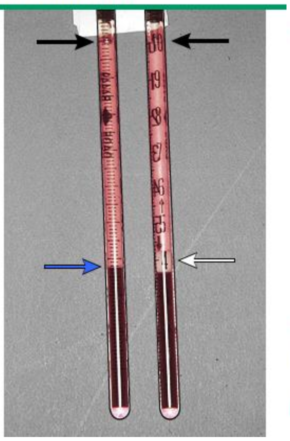


Blood smear from a patient with megaloblastic anemia showing a neutrophil with an increased number of nuclear lobes. At least six discrete lobes are present; normal neutrophils have five lobes or fewer.

Megaloblastic blood picture



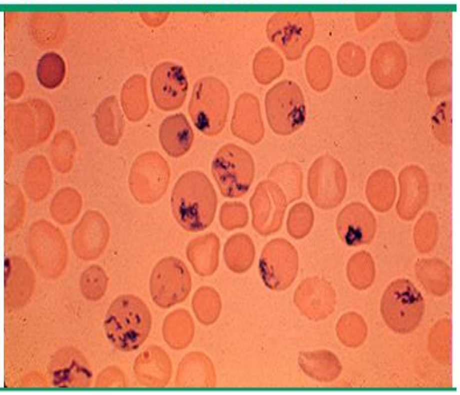
Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macro-ovalocytes, a pattern that can be seen with cobalamin or folate deficiency.


Manual (spun) hematocrit

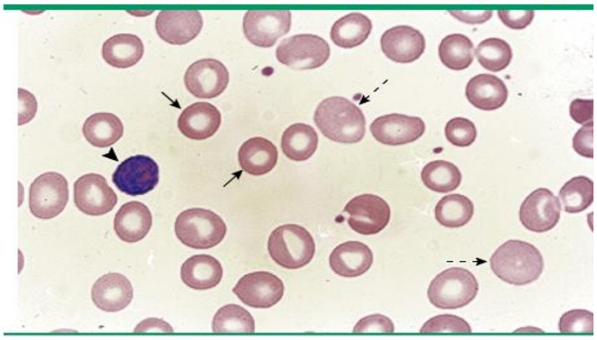
Microhematocrit determination

The capillary tube is plugged at one end and centrifuged (left). The proportion of blood volume occupied by red cells can be readily determined by eye in a microhematocrit reader (right).

This photo(left) shows two anticoagulated blood-filled Wintrobe hematocrit tubes following high speed centrifugation. The tube on the left is from a normal subject, with a hematocrit of 38 percent (blue arrow). The tube on the right is from a 19-year-old female with essential thrombocytosis, a normal white blood cell count, and a platelet count of 5,000,000/microL. The extreme degree of thrombocytosis can be appreciated by the presence of a marked increase in the size of the "buffy coat" (white arrow). When the Wintrobe tube is filled to near capacity (upper arrows), and the white blood cell count is not markedly elevated, the platelet count can be estimated by the thickness of this layer, with each mm being equivalent to one million platelets/microL. In normal subjects, the buffy coat, which is comprised of white blood cells and platelets, is only minimally visible.

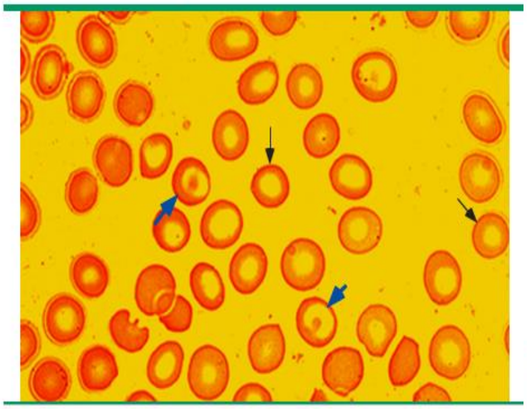

Reticulocytes after supravital staining

Supravital stain of a peripheral blood smear shows blue-stained residual reticulin (ribosomal RNA) in reticulocytes.


Polychromatophilia due to increased reticulocytes

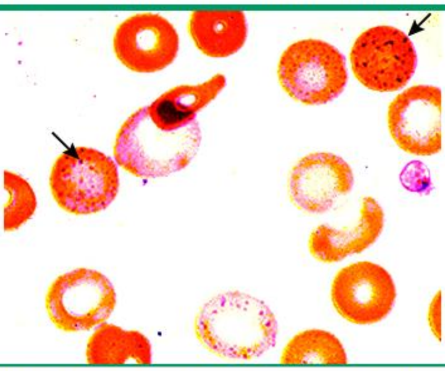
Peripheral blood smear taken from a patient with increased reticulocytes. Unlike mature red cells (arrows), which have central pallor and are the same size as the nucleus of a small lymphocyte (arrowhead), reticulocytes (dashed arrows) are larger, have a blue tint, and lack central pallor because they are not biconcave discs. (Wright-Giemsa stain.)

Beta thalassemia trait



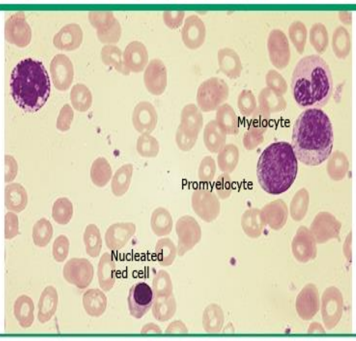
Peripheral smear from a patient with beta thalassemia trait. The field shows numerous hypochromic and microcytic red cells (thin arrows), some of which are also target cells (blue arrows).

Basophilic stippling of red cells in lead poisoning



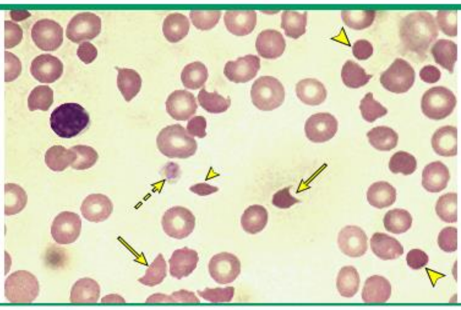
Peripheral blood smear shows basophilic stippling in several red cells from a patient with lead poisoning. The granules represent ribosomal precipitates. A similar picture can be seen in a number of other conditions including thalassemia, megaloblastic anemia, sickle cell anemia, and sideroblastic anemia.

Leukoerythroblastic peripheral blood smear



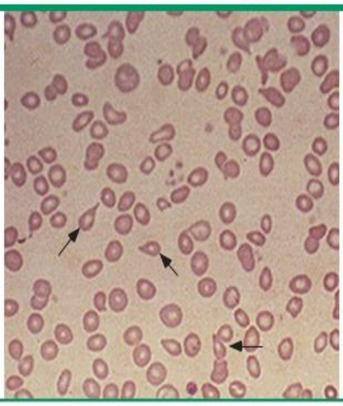
Leukoerythroblastic peripheral blood smear showing the presence of nucleated red cells and immature white cells. This pattern occurs with marrow replacement, usually due to fibrosis that may be idiopathic (eg, primary myelofibrosis) or reactive to conditions such as metastatic cancer.

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes



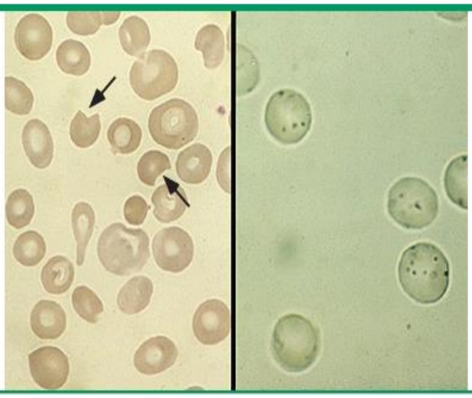
Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Teardrop-shaped red blood cells (dacrocytes)



This peripheral smear from a patient with bone marrow fibrosis shows numerous teardrop-shaped red cells (arrows). Note that the teardrops are pointed in several different directions, ruling out an artifact due to preparation of the smear.

Peripheral smear in Heinz body hemolytic anemia showing Heinz bodies and bite cells



Split screen view of a peripheral smear from a patient with Heinz body hemolytic anemia. Left panel: red cells with characteristic bite-like deformity (arrows). Right panel: Heinz body preparation that reveals the denatured hemoglobin precipitates.

4) Further investigations: depends on the suspected cause/s of anemia based on the above tests, the history and physical examination findings.

- **Suspected iron deficiency anemia**:
  - ✓ Serum **ferritin**
  - ✓ Total iron binding capacity **(TIBC)**
  - ✓ Transferrin saturation = $\frac{\textbf{Serum Iron}}{\textbf{TIBC}} X\ 100\ \%$, TIBC = Total Iron binding capacity

  Once iron deficiency is diagnosed:
  - ✓ Stool for **occult blood**
  - ✓ Stool microscopy for **hookworm** infestation
  - ✓ **Upper GI endoscopy or colonoscopy** may be needed based on the clinical suspicion.
- **Suspected megaloblastic anemia**:
  - ✓ serum vitamin B12 level
  - ✓ serum folate
- **Suspected hemolytic anemia**:
  - ✓ Reticulocyte count or percentage bilirubin (indirect hyperalbuminemia)
  - ✓ LDH
  - ✓ Coomb's test

Treatment

Non pharmacologic

- **Transfusion** of packed RBC:
- Indications for transfusion
  - ✓ Hemoglobin $\leq$ 7g/dl → for most hospitalized patients
    - For ambulatory patients with chronic anemia transfusion may not be needed even at hemoglobin is <7g/dl, unless the patients have severe symptoms e.g. heart failure
  - ✓ Hemoglobin $\leq$ 8g/dl → for those with pre-existing chronic cardiac disease, undergoing orthopedic or cardiac surgery
  - ✓ In trauma or acutely bleeding patients
    - Do not use hemoglobin or hematocrit for transfusion decision as they are falsely elevated
    - Hemodynamic status and ongoing nature of bleeding should be used
    - **Whole blood is preferable if there is acute or ongoing bleeding**

  - For the following patient's higher hemoglobin target might be aimed
    - Acute coronary syndrome
    - Severe thrombocytopenia in hematology/hematology patients
- **Nutritional support**

Pharmacologic

- Depends on the underlying cause of anemia.
- Patients with anemia suspected due to primary bone marrow disease, malignancy, autoimmune disease, GI bleeding, and unknown/unclear cause should get further management at referral hospital level.

3.12.1.1 Iron deficiency anemia (IDA)

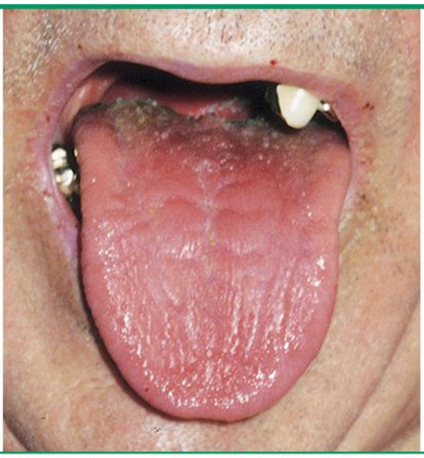
- IDA is a common cause of anemia worldwide.
- The major causes of IDA are
  - nutritional deficiency
  - impaired absorption from the GI tract
  - chronic blood loss from the GI or genitourinary tract caused by:
    - hook worm infestation
    - colonic cancer
    - bleeding peptic ulcer or gastric cancer
    - prolonged or excessive menstrual bleeding
    - gynecologic malignancies etc.

Clinical features

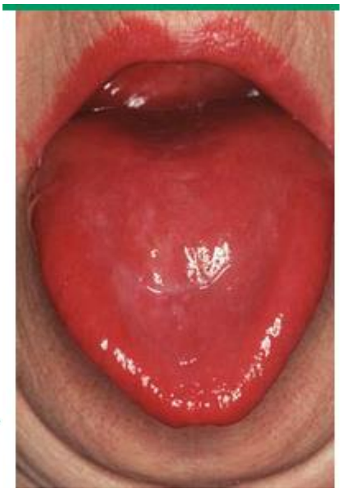
- In addition to the general clinical features anemia (mentioned above), chronic IDA might show unique clinical features.
  - Pica: desire (craving) to eat unusual substances like soil, ice.
  - Koilonychia: Thin, brittle nail with depressed (concave or spoon) distal half.
  - Cheilosis (also called angular cheilitis), Glossitis or angular stomatitis: the tongue and angel the mouth inflamed and sore,
  - Atrophic glossitis with loss of tongue papillae, which may be accompanied by tongue pain or dry mouth
  - Alopecia (rare) in especially severe cases
  - Chlorosis (pale, faintly green complexion; extremely rare)
  - Esophageal web, which may be accompanied by dysphagia (e.g. Plummer-Vinson or Patterson-Kelly syndrome; rare)

- ✓ Restless legs syndrome (RLS), also called Willis-Ekbom disease (WED)

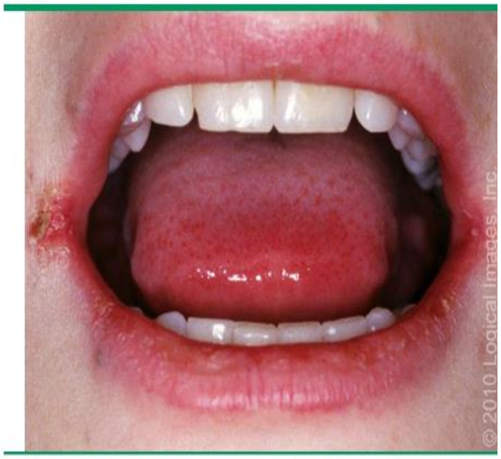
Atrophic glossitis



A smooth tongue that has lost its papillae and is often sore suggest a deficiency in riboflavin, niacin, folic acid, vitamin B12, or iron. This patient had vitamin B12 deficiency.

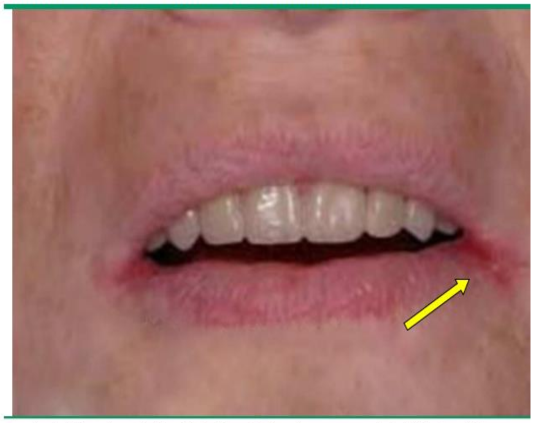


Angular cheilitis



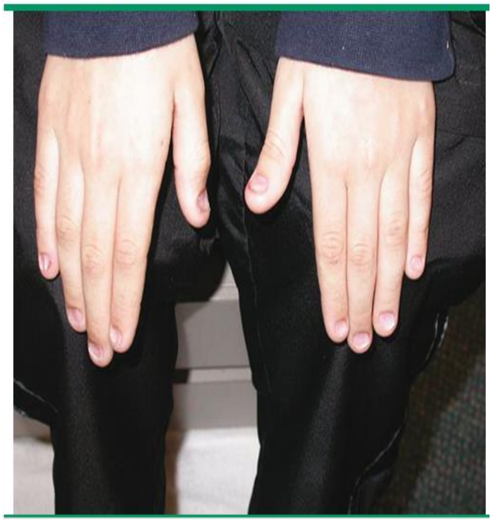
Erythema and fissures are present at the corners of the mouth.

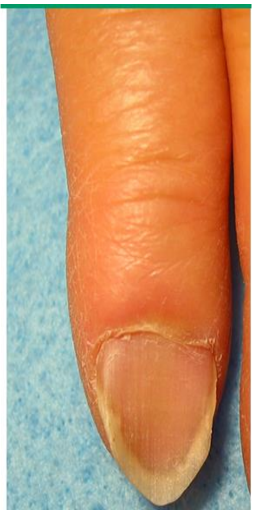
Angular cheilitis in a patient with iron deficiency



Angular cheilitis, also called "perlèche," is a finding that may occur in individuals with iron deficiency. Refer to UpToDate topics on the clinical manifestations of iron deficiency for additional clinical findings, and on cheilitis for additional causes of cheilitis.

Koilonychia (spoon nail) associated with iron deficiency





Investigations specific for IDA

- CBC: low Hg and hematocrit, low MCV, low MCH, and increased RDW.
- PM; microcystic hypochromic anemia (look at images above)
- Iron studies
  - ✓ Serum Ferritin → usually low (it could be high in patients with chronic inflammation or CKD in spite of iron deficiency)
  - ✓ Serum iron → may be low or normal
  - ✓ Total iron binding capacity (TIBC)→ usually high
  - ✓ Transferrin saturation (TSAT) = $\frac{\textbf{Serum Iron}}{\textbf{TIBC}}\ x\ \mathbf{100}$ %; low (<20%)
- Clinical evaluation and investigation to identify the possible cause of bleeding
  - ✓ Stool for ova of parasites
  - ✓ Digital rectal examination
  - ✓ Gynecologic examination
  - ✓ Upper GI endoscopy and/or colonoscopy.

Treatment of IDA

- **Treatment of the underlying cause**
  - ✓ The cause of the iron deficiency state should be identified and treated.
- **Oral iron (tablet): For at least 3 months following correction of the anemia**
  - ✓ **Ferrous sulfate,** 325mg (has 65mg elemental iron), PO, TID. OR
  - ✓ **Ferrous fumarate,** 325mg, (has 107 elemental iron), PO, BID. OR
  - ✓ **Ferrous gluconate**, 325mg P.O. (39mg elemental iron), 1-2tabs, TID
- **Oral iron (solutions/syrup):** if the tablets are not tolerated or patient preference
  - ✓ **Iron hydroxide polymaltose syrup (**50mg/5ml of elemental iron), 10ml PO, BID to TID. OR
  - ✓ **Ferrous gluconate syrup** (24mg/5ml of elemental iron),15ml, PO TID. OR
  - ✓ **Ferric ammonium citrate syrup** (32.8mg/15ml of elemental iron), give 30ml, TID.

How to instruct oral iron intake?

- Preferably to be taken **2 hours before or 4 hours after meal**.
- **If separating from food is difficult** due to gastrointestinal side effects, foods which significantly interfere with iron absorption should be **avoided** when the iron is given e.g. **milk, eggs, tea, and coffee**.
- GI side effects are very common with oral iron administration. These include epigastric pain, nausea or vomiting, constipation or diarrhea, metallic taste.
- For patients who do not tolerate, they may be advised to take it with meals, or to take a smaller dose, solutions or elixir forms.

Intravenous (IV) iron

- **Indications** for IV iron therapy
  - ✓ Intolerance to oral iron therapy.
  - ✓ Anemia secondary to CKD with a requirement for erythropoietin.
  - ✓ No improvement in hemoglobin after 4 weeks of oral iron.
  - ✓ Existence of conditions that interfere with absorption of iron from the GI tract e.g. atrophic gastritis, gastrectomy, inflammatory bowel disease
  - ✓ Blood loss difficult to cope with oral iron therapy e.g. heavy menstrual bleeding, bleeding telangiectasia
  - ✓ Severe anemia during late 2nd or 3rd trimester of pregnancy

- **IV iron administration**
  - ✓ **For patients not on hemodialysis:**
    - **Iron sucrose** 200mg, IV, administer over 5 minutes, every 3 days for a total of 5 doses (a total of 1g).
      - This dose is usually sufficient but if hemoglobin is not corrected, additional doses can be given.

      OR
    - **Iron sucrose** 200mg diluted in 100ml NS; administer over 30 minutes.
  - ✓ **For patients on hemodialysis**
    - **Iron sucrose** 100mg, IV, over 2-5 minutes, given early during dialysis sessions (within the first hour) until iron deficiency is corrected. It needs to be given again, if iron deficiency persists or recurs.

N.B Patients with iron deficiency anemia due to GI bleeding or unknown cause or those with known reversible cause but refractory to iron therapy should get further management at referral hospital level.

3.12.1.2 Megaloblastic anemia

- Megaloblastic anemia is a morphologic term that describes abnormal red blood cells with maturation defects; the red blood cells tend to be large.
- The major causes of megaloblastic anemia are vitamin B12 (Cobalamin) and folate deficiency or a combination of both
- The pathologic process which results in megaloblastic anemia can also result in leukopenia and thrombocytopenia. In case of Vitamin B12 deficiency the nervous system can be affected.

Causes of megaloblastic anemia

- **Major causes of vitamin B12 deficiency**
  - ✓ Gastric origin (pernicious anemia, chronic atrophic gastritis)
  - ✓ Small intestine malabsorption (chronic diarrhea from small bowel/ileal pathologies)
  - ✓ Strict vegetarians.
- **Major causes of folate deficiency**
  - ✓ Poor nutritional status
  - ✓ Increased demand during pregnancy and lactation
  - ✓ Alcoholism
  - ✓ Drugs: anti-epileptic drugs (phenytoin, phenobarbitone) or drugs which affect Folate metabolism (Methotrexate, cotrimoxazole)
  - ✓ Malabsorption
  - ✓ Critical illness.

Clinical features

- In addition to the clinical features of anemia due to any other cause, some clinical manifestations may suggest megaloblastic anemia.
  - ✓ Glossitis (pain over the tongue with smooth, beefy red tongue)
  - ✓ Angular cheilitis
  - ✓ Jaundice
  - ✓ **Neurologic or neuropsychiatric manifestation: specific to vitamin B12** deficiency, but not folate deficiency
    - Neuropathic pain in the lower limbs
    - Decreased position sensation and gait disturbance
    - Weakness of the lower extremities
    - Irritability, depression, disorientation, dementia, frank psychosis

Investigations for megaloblastic anemia

- CBC
  - ✓ Anemia with high MCV (>100fl). When there is concomitant iron deficiency, the MCV can be normal or low.
  - ✓ Leukopenia and thrombocytopenia may also be found.
  - ✓ Peripheral morphology: hyper segmentation of neutrophils, large RBCs (macro-ovalocytes) → look at image above
  - ✓ Hyper segmentation of neutrophils is defined as >5% of neutrophils with 5 or more lobes.
- Bilirubin: Indirect hyperbilirubinemia
- Determination of the levels of vitamin B12 and Folate
  - ✓ Serum vitamin B12 level
  - ✓ Serum folate level
  - ✓ RBC folate level: to be requested if serum folate level is normal
- Bone marrow aspiration: indications
  - ✓ If the serum vitamin B12 and folate levels are normal but there is strong clinical suspicion.
  - ✓ When there is need to exclude other causes.
- Determining the cause of the deficiency: if the cause is not clinically obvious, further wok up will be needed to identify the underlying cause.

Treatment

Treatment of vitamin B12 (Cobalamin) deficiency

- **Cyanocobalamin (Vitamin B12)** 1000μg (1mg), IM, to be given according to the following schedule
  - ✓ Every day for one week
  - ✓ Every week for four weeks. If hemoglobin has not normalized, continue weekly until it gets normal.
  - ✓ If the underlying disorder persists, 1mg every month for the rest of the patient's life.

Treatment of folate deficiency

- **Folic acid**, 1 to 5mg P.O., daily for 1-4 months, or until complete hematologic recovery.

- ✓ Vitamin B12 level should be checked before giving folic acid alone; as treatment with folic acid alone might worsen neurologic manifestation of vitamin B12 deficiency.
- ✓ If vitamin B12 can't be checked, both Folic acid and vitamin B12 should be started at the same time.

Follow up of treatment response

- ✓ Symptomatic improvement
- ✓ Hemoglobin level

Patients with the following conditions need special care with hematology and gastroenterology services

- ✓ If the underlying cause is not clinically obvious.
- ✓ If other causes of anemia/cytopenia cannot be excluded.
- ✓ Lack of response to the treatment provided.

3.12.2 Blood Transfusion

Indications for blood transfusion

Table; Thresholds for red blood cell transfusion in adults

Condition		Hemoglobin threshold for transfusion
Symptomatic patient (eg, myocardial ischemia)		10 g/dL
Hospitalized patient	Preexisting coronary artery disease	8 g/dl
	Acute coronary syndromes	8 to 10 g/dL
	ICU (hemodynamically stable)	7 g/dl
	GI bleeding (hemodynamically stable)	7 g/dL
	Cardiac surgery	7.5 g/dL
	Non-cardiac surgery	8 g/dL
Ambulatory outpatient	Oncology patient in treatment	7 to 8 g/dl
	Palliative care setting	As needed for symptoms; hospice benefits may vary

- ➢ for Acute blood loss;
  - ✓ Do not use hemoglobin or hematocrit for transfusion decision as they are falsely elevated.
  - ✓ Hemodynamic status and ongoing nature of bleeding should be used
  - ✓ Whole blood is preferable if there is acute or ongoing bleeding

Practical points about transfusion (especially for medical interns and ward Nurses)

- **Consent** → Informed consent for RBC transfusion should be obtained from the intended recipient before all non-emergent administration of blood components. According to AABB standards, elements of consent should include: a description of the risks, benefits, and treatment alternatives; the opportunity for the intended recipient to ask questions; and the right of the patient to accept or refuse transfusion.
- After determining patient M.HCT, 1st send blood sample for **cross match** (if BG &Rh is unknown, request ''BG& Rh with cross match'', if BG is known, write pt's BG and Rh on request paper and request cross match)
- During transfusion, **keep the Patient NPO**, **discontinue any medication** (either Parenteral or oral) until transfusion is finished
- **Check the blood unit bag** about expire date, major/minor reaction, compare the bag number with the number written on transfusion request paper
- For patients who require blood that is warmed (e.g. those at risk of hypothermia or autoimmune cold-induced hemolysis), put the blood out of the cold box keep covered with clothes at the bedside, that raise the temperature closer to body temperature are used. Avoid heating of the blood cells above 40°C, which will cause hemolysis
- **Use Green IV cannula** for transfusion
- Transfusion **one unit should be completed within 3 hours** but not less than one hour (faster rate may be needed in acute blood loss)
    - ✓ Infusion rate →**Suggested rates for adults are 20 to 40 drops per minute for the first 15 minutes and then as rapidly as tolerated;**
    - ✓ **The complete infusion should not exceed 4 hours.** However, slower rates of infusion (possibly combined with administration of a smaller unit to comply with the four-hour infusion requirement) and/or the **administration of diuretics may be indicated for patients who are predisposed to circulatory overload.**
    - ✓ the dose of transfusion for Neonates is 20ml/kg, less than 7 days old over 3hr (Acute blood loss - Whole blood 20ml/kg less than 7 days old over 1 hour.)
- **follow with transfusion follow up sheet**
- **finally, document ''transfusion completed without complication at ''X'' DLT/NLT''**
- Blood transfusion follow up sheet (include blood component E.g. Whole blood transfussion follow up sheet)

Blood transfusion follow up sheet															
Date	time	BP	PR	RR	T^0	SaO_2	JVP	S3 gallop	Liver size	Basal rales	itching	rash	Input	output	sign

- Check post transfusion M.HCT of last transfusion (the usual trend in our set up is after 8hour)
  - ✓ UpToDate 2018 says *''The post-transfusion hemoglobin level may be accurately measured as early as 15 minutes following transfusion, as long as the patient is not actively bleeding. This practice is based on studies showing a high degree of concordance between values measured 15 minutes after the transfusion versus longer intervals''.*
  - ✓ **Each unit** of packed red blood cells (RBCs) contains approximately 200 mL of red cells and, in an adult, **will raise the hematocrit by roughly 3 % points** unless there is continued bleeding.
- Within one day, it is better not to transfuse more than 3 units of blood unless there is life threating condition (e.g. massive bleeding, active and uncontrolled Upper GI bleeding)
- Observation following transfusion
  - ✓ In addition to observing the patient during transfusion, continue observing for 15 to 30 minutes post-transfusion.

Complications of Transfusion

Complications from a single transfusion

- **ABO incompatibility**
  - ✓ Clinical presentation=hematuria, bilateral flank pain, fever, chills, rigor, oliguria (ATN)
  - ✓ Rx=stop blood transfusion. send it to blood bank & recheck
    - Repeat coagulation profile
    - Iv fluids, monitor UOP, U/A for Hgb
    - Diuretic- furosemide
- **Minor incompatibility reaction**
  - ✓ Due to extra vascular hemolysis (mild, occur in 2-21days)
  - ✓ Clinical presentation-fever, malaise & jaundice
  - ✓ Rx-supportive
- **Febrile reaction**
  - ✓ Due to sensitization to WBCs or platelets
  - ✓ increase temperature but no hemolysis
  - ✓ Use of 20-40mm filter or leukocyte depleted blood avoids it.
- **Allergic reaction**
  - ✓ Due to allergy to plasma products
  - ✓ Clinical presentation - chills, rigor & rash
  - ✓ Rx- antihistamines
- **Embolism**

- ✓ Although air embolism has been reported as a complication, healthy individuals can tolerate large amounts of air injected intravenously at a rapid rate.
- ✓ The normal adult can tolerate an embolism of 200 mL of air.
- ✓ Smaller amounts, however, can cause alarming signs.
- ✓ Manifestations of venous air embolism include a rise in venous pressure, cyanosis, a "mill wheel murmur", tachycardia, hypotension, and syncope.
- ✓ Treatment - consist of placing the patient on the left side in a head down position with the feet up.
- ✓ Arterial air embolism may be visible in the retinal vessels or as blood flows from transected vessels.
- ✓ Plastic tubes used for transfusion can break off within a vein and embolize into the right atrium or pulmonary artery.
- ✓ Embolized catheters have been successfully removed.

- ➢ **Thrombophlebitis**
  - ✓ Prolonged infusions into a peripheral vein are associated with venous thrombosis.
  - ✓ Intravenous infusions that last more than 8 hours are more likely to be followed by thrombophlebitis, with an increased incidence in the lower limbs.
  - ✓ Treatment consists of discontinuation of the infusion and the application locally of warm moist compresses.
  - ✓ Embolization from superficial thrombophlebitis or venous thrombosis is extremely rare.
- ➢ **Over transfusion and Pulmonary Edema**
  - ✓ **Volume overload is typically a concern in the elderly, small children, and those with compromised cardiac function.**
  - ✓ Overloading the circulation is an avoidable complication.
  - ✓ It can occur with rapid infusion of blood, plasma expanders, and other fluids, particularly in patients with heart disease.
  - ✓ To prevent the complication, the central venous pressure should be measured whenever large amounts of fluid are administered.
  - ✓ Circulatory overload is manifested by a rise in venous pressure, dyspnea, and cough.
  - ✓ Rales can generally be heard at the lung bases.
  - ✓ Treatment consists of diuresis, placing the patient in a sitting position, and, occasionally, venesection.

- ➢ **TRALI (transfusion-related acute lung injury)**
  - ✓ It is sometimes seen after transfusion and is characterized as mild to life-threatening.
  - ✓ Noncardiogenic pulmonary edema is often accompanied by fever, rigors, and a "white out" chest x-ray.

  - ✓ Treatment is discontinuation of any transfusion, notification of the transfusion service, and intensive pulmonary support, sometimes including intubation.
  - ✓ This type of pulmonary edema does not respond to diuretics and is thought to be caused by infused donor antigranulocyte or anticlass I or II MHC antibodies.
- **Infection**
  - ✓ Bacterial infection
    - contamination of infused blood is rare and can be acquired from contaminated collection bags or poor cleaning of the donor's skin.
    - Gram-negative organisms, especially coliform and Pseudomonas species, which are capable of growth at 4^0C (39.2^0F), are the most common cause.
    - Clinical manifestations include
      - fever, chills, abdominal cramps, vomiting, and diarrhea.
      - There may be hemorrhagic manifestations and increased bleeding.
    - If the diagnosis is suspected, the transfusion should be discontinued and the blood cultured.
    - Emergency treatment includes oxygen, adrenergic blocking agents, and antibiotics.
  - ✓ Hepatitis, HIV, malaria, syphilis.
    - It is mandatory to screen the blood for these diseases before transfusion.

Complications from massive transfusion

- Massive transfusion, historically defined as the replacement by **transfusion of 10 units of red cells in 24 hours**, is a response to massive and uncontrolled hemorrhage. With more rapid and effective therapy, **alternative definitions such as 3 units over 1 hour** are more sensitive in identifying patients needing rapid issue of blood products for serious injuries because of uncontrolled hemorrhage
- Such transfusion episodes are associated with a number of hemostatic and metabolic complications.
- Massive transfusion involves the selection of the appropriate amounts and types of blood components to be administered, and requires consideration of a number of issues including volume status, tissue oxygenation, management of bleeding and coagulation abnormalities, as well as changes in ionized calcium, potassium, and acid-base balance.

Complications include;

- Allergic and immune transfusion reactions can occur in any patient, and are more common in multiply-transfused patients. including TRALI
- Coagulopathy
- Hypocalcaemia

- Hyperkalaemia/ Hypokalaemia
    - ✓ Hyperkalemia from potassium released from RBCs during blood bank storage is primarily a concern in massive transfusion, impaired renal function, and infants/newborns.
- Hypothermia
- Iron overload
    - ✓ Iron overload becomes a concern after a large number of transfusions for chronic anemia.
    - ✓ Each transfused unit of RBCs contains 250 mg of elemental iron

Blood components

Banked Whole Blood

- ✓ With the new preservatives, the shelf life has been extended to 40 ± 5 days.
- ✓ At least 70% of the transfused erythrocytes remain in the circulation for 24 hours after transfusion and are viable.
- ✓ The hemolysis that occurs during storage is insignificant.
- ✓ Preferred for anemia with volume depletion

Fresh Whole Blood

- ✓ Refers to blood that is administered within 24 hours of its donation and is rarely indicated.
- ✓ Because of the time required for testing for infectious disease, it must be administered untested.
- ✓ One unit of platelet concentrate has more viable platelets than 1 unit of fresh blood.
- ✓ Fresh whole blood is a poor source of platelets and factor VIII.
- ✓ Preferred for neonates

Packed RBC (Red Blood Cells)

- ✓ The major difference between packed RBCs and whole blood is the volume of plasma present in the unit of blood.
- ✓ **Patients with chronic anemia should be transfused with Packed RBC** since volume replacement is not required.
- ✓ Furthermore, since the patient already has an expanded blood volume to compensate for the anemia, circulatory overload may be a risk if plasma is also given.
- ✓ Cells are spun down and concentrated.
- ✓ Each unit = 330 ml (Hct=50 - 70%)
- ✓ Packed RBCs are stored in a SAG-M solution (saline—adenine—glucose—mannitol) to increase shelf-life to 5 weeks at 2 - 6^0C.

- **Fresh-frozen plasma (FFP)**
  - ✓ It is rich in coagulation factors & removed from fresh blood and stored at -40 to -50^{0}C with a 2 years shelf-life.
  - ✓ It is the first-line therapy in the treatment of coagulopathic hemorrhage.

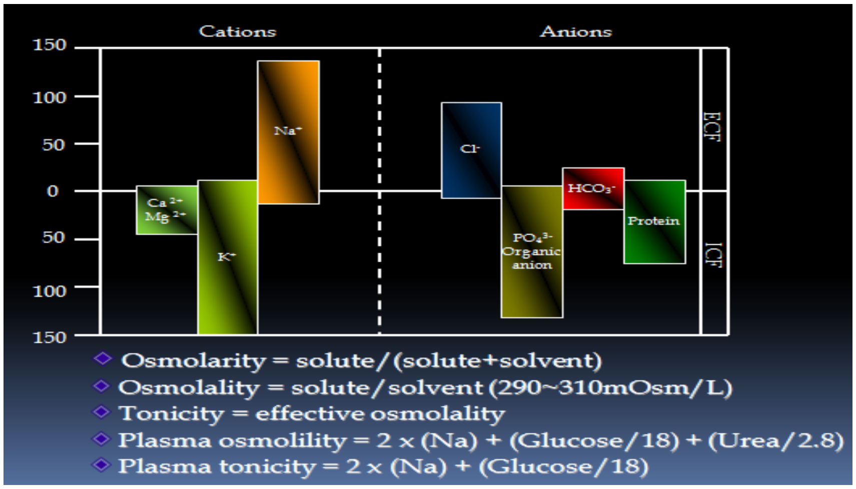
- **Platelet**
  - ✓ Pooled platelet concentrate containing about 250 x10^9 cells/L.
  - ✓ Platelets are stored on a special agitator at 20 - 24 ^{0}C and have a shelf-life of only 5 days.
- **Cryoprecipitate**
  - ✓ It is precipitate of FFP
  - ✓ Rich in factor VIII and fibrinogen
  - ✓ Stored at -30^{0}C with a 2-year shelf-life
  - ✓ Given in low-fibrinogen states or in factor VIII deficiency

- **Prothrombin complex concentrate**
  - ✓ Contain factors II, IX and X (factor VII may be included)
  - ✓ Indicated for the emergency reversal of anti-coagulant (warfarin) therapy in uncontrolled haemorrhage

3.12.3 Fluid and electrolyte disturbance

3.12.3.1 Fluid, Maintenance Fluid (MF) calculation

Composition of body fluids



- Osmolarity = solute/(solute+solvent)
- Osmolality = solute/solvent (290~310mOsm/L)
- Tonicity = effective osmolality
- Plasma osmolility = 2 x (Na) + (Glucose/18) + (Urea/2.8)
- Plasma tonicity = 2 x (Na) + (Glucose/18)

Total Body Water (TBW)

- 60% in an average young adult male & 50% in young adult female

- The highest percentage of TBW is found in newborns, with approximately 80% of their total body weight.

Fluid Balance

- Fluid and electrolyte homeostasis is maintained in the body
- Neutral balance: input = output
- Positive balance: input > output
- Negative balance: input < output
- Na+ is the major extracellular cation & K+ major intracellular cation
- **Fluid balance is made through vasopressin, water ingestion & renal water transport to keep osmolality 280-295 mosm/kg**

Types of crystalloids

- RL (ringer lactate)
  - ✓ Slightly hypotonic in that it contains 130 mEq of lactate.
  - ✓ It is ideal for the replacement of existing fluid deficits when serum electrolyte concentrations are normal. Because Lactate is used rather than bicarbonate because it is more stable in IV fluids during storage. It is converted into bicarbonate (used to buffer acid base imbalance) by the liver after infusion, even in the face of hemorrhagic shock.
- NS (normal saline /Sodium chloride (0.9%))
  - ✓ **It** is mildly hypertonic, containing 154 mEq of sodium that is balanced by 154 mEq of chloride
  - ✓ The high chloride concentration imposes a significant chloride load on the kidneys and may lead to a hyperchloremic metabolic acidosis.
  - ✓ So, it is an ideal solution, for correcting volume deficits associated with hyponatremia, hypochloremia, and metabolic alkaloids
- D5W (5% dextrose)
  - ✓ 50 g of dextrose per liter--supplies 200 kcal/L
  - ✓ Dextrose is always added to solutions containing <0.45% sodium chloride (hypotonic) to maintain osmolality and thus prevent the lysis of RBCs that may occur with rapid infusion of hypotonic fluids. The addition of potassium is useful once adequate renal function and urine output are established.

- 0.45% sodium chloride
  - ✓ useful for replacement of ongoing GI losses as well
  - ✓ This solution provides sufficient free water for insensible losses and enough sodium to aid the kidneys in adjustment of serum sodium levels.
  - ✓ This hypotonic solution causes lysis of RBCs--to prevent this add 5% dextrose (50 g of dextrose per liter)

- DNS → contains 5% dextrose and NS, important for transition phase of DKA mgt

Alternative Resuscitative Fluids

- Hypertonic saline
  - ✓ Hypertonic saline solutions (3.5% and 5%) → used for correction of severe sodium deficits
  - ✓ Hypertonic saline (7.5%)

colloids

- Four major types of colloids are available
  - ✓ Albumin
  - ✓ Dextrans
  - ✓ hetastarch, and
  - ✓ Gelatin

Disorders	Fluid of choice
Diarrhea	RL
Vomiting	NS
DKA	
Sepsis	Crystalloid

Maintenance Fluid (MF) calculation

- It is the usual daily requirement. It to replace basal fluid requirement i.e the sensible and insensible losses
- Calculation of MF replacement doesn't include replacement of either preexisting deficits or ongoing additional losses

Maintenance fluid calculation	
Weight in kg	Amount of fluid /kg/day
0-10 kg	100 ml/kg/day
11-20 kg	1000ml (100 X the 1st 10 kg) + 50 ml/kg/day for the next kg
>20 kg	1500ml (100 X the 1st 10 kg + 50 x the 2nd 10kg) + 20 ml/kg/day for the remaining kg

- E.g. MF for 70kg pt (10kgX100ml +10kgX50ml+50kgX20ml) = 2500ml per day (i.e 2500 ml over 24hrs)
- To run over 8hours divide the total MF for 3 (since 24hr ÷ 3 = 8hrs). So, for this pt, 2500ml /3 = 833 ml over 8hrs
  - ✓ 1ml=20drops through IV line
  - ✓ 8hrs=8X60min=480 min
- If we want 833ml over 480min (meaning 8 hrs), we have to adjust by calculating the drop as follows

$$\text{MF} = \frac{833\text{ml x 20 drops}}{8hrs\ x\ 60min} = \frac{16{,}660\text{ drops}}{480\ min} = 35 \text{ drops per minute}$$

- What are the fluid components for MF?
  - 1/3rd of total MF is NS and 2/3rd D10
  - D10 = 85% of D5 + 15 % of D40
- For the above patient
  - 1/3rd of 833ml = 278ml of NS, 2/3rd of 833ml = 555 ml of D10
  - 85% of 555ml D10 = 472ml D5, 15 % of 555ml D10 = 83ml D40
- So, your order could be like this
  - Put on MF (278ml of NS + 472ml D5 + 83ml D40) to run over 8 hrs at a rate of 35 dpm
  - This numbers may be difficult to give practically. So, the order can be modified as Put on MF (280ml of NS + 470ml D5 + 80ml D40) to run over 8 hrs at a rate of 35 dpm
  - The usual trend of MF, for adult, in our setup is; 3 vials of D40 in 1L of NS to run over 8hr (@40 dpm) → please don't practice like this
- How do we know that, D10 = 85% of D5 + 15 % of D40?

Fluid preparation

- Fluid is available in the form of 5% DW, 40% DW, 9% NS, or RL, but there is no readily prepared fluid 10% DW (D10) in most setups of Ethiopia.
- We have to prepare fluid using what is available. To prepare fluid, use following formula. We need to prepare x% DW from a% DW and b% DW

  $Vb = \frac{(a-x)\ x\ Tv.}{(a-x)+(x-b)}$, $Va = \frac{(X-b)\ x\ Tv.}{(a-x)+(x-b)}$

  (Where x = conc. of DW wanted, a = highest conc. of DW , b = lowest conc. of DW, Va = volume of a, Vb = volume of b, Tv = total volume needed = Vb + Va)
- For example: How to prepare Total volume (Tv) of 10%DW from 40%DW & 5% DW.
  - **Given** x = 10%, a = 40, b = 5% , Va = volume of 40%, Vb = Volume of 5%, Tv = total volume needed = (Vb + Va)
  - $Vb = \frac{(40-10)\ x\ Tv.}{(40-10)+(10-5)}$, $Va = \frac{(10-5)\ x\ Tv.}{(40-10)+(10-5)}$
  - $Vb = \frac{30\ x\ Tv.}{35}$, $Va = \frac{5\ x\ Tv.}{35}$
  - **Vb (D5W) = 0.85 (meaning 85%) x Tv (D10), Va (D40) = 0.15 (meaning 15%) x Tv (D10)**

3.12.3.2 Electrolyte disturbance

1) Hypokalaemia

- Hypokalemia is defined as serum potassium level < 3.5mmo/l.

Potassium	Value (in mmol/L or meq/l)

Normal	3.5 - 5.0
Mild hypokalemia	3.0 - 3.5
Moderate hypokalemia	2.5 - 3.0
severe hypokalemia	< 2.5

Causes of Hypokalemia

- Hypokalemia is either caused by loss from the body or entrance (shift) of the plasma potassium in to the cell (intracellular compartment)
- **Causes due to potassium loss**
  - ✓ Renal loss:
    - Diuretics, DKA, resolving AKI/obstructive uropathy, prolonged vomiting or NG tube drainage
    - Hypomagnesemia, renal tubular disorders due to drugs like aminoglycosides, amphotericin, tenofovir, inherited tubular diseases
    - Hyperaldosteronism
  - ✓ GI loss: diarrhea
- **Causes due to redistribution/shift into intracellular space**
  - ✓ Medicines: Insulin, beta-2 agonists
  - ✓ Metabolic alkalosis

Clinical features

- Unless it is severe, Mild to moderate hypokalemia is generally asymptomatic.
- If there are symptoms attributable to hypokalemia, it is considered to be severe.
- Symptoms of muscle weakness:
  - ✓ Weakness of extremities
  - ✓ Abdominal distention
- Neuromuscular
  - ✓ Generalized fatigue and malaise
  - ✓ Muscle cramps, paresthesia
  - ✓ Severe weakness (K <2.5 mEq/L)
  - ✓ Paralysis if K <2.0 mEq/L and rapid development
- CVS: ventricular or atrial arrythmia: the most feared manifestation of hypokalemia is ventricular arrhythmia, as it is sudden onset there might not be any signs during evaluation, cardiac arrest
- GIT: Constipation, ileus, Gaseous abdominal distention with decreased to absent bowel sounds and failure to pass feces due to paralytic ileus
- GUS: Polyuria (hypokalemic nephropathy)

- Rarely features of rhabdomyolysis: muscle weakness, pain and dark urine
- life-threatening complications are arrhythmias and paralysis

Investigations and diagnosis

Diagnosis

- The diagnosis is made based of serum potassium determination.
- ECG is needed to assess the severity

Investigations

- Electrolytes → Serum potassium, Serum magnesium, serum Ca
- ECG
- Further investigations to determine the underlying cause might be needed if the cause is not obvious like Cr and BUN, serum osmolality, urine PH, Urine K

Treatment

- Total body deficit is 200-300 mEq per 1 mEq/L decrement in serum K+ level
- Rate and route dependent on presence of symptoms, severity of hypokalemia, and comorbidities
- Complete replacement over several days
- Oral potassium preferable to IV therapy whenever possible

Non pharmacologic treatment

- Encourage foods rich in potassium e.g. Peanut butter, avocado, bananas, orange juice, papaya.
- Avoid exercise in patients with moderate to severe hypokalemia

Pharmacologic treatment

Severe hypokalemia

- Potassium chloride **(KCl) IV infusion**. 40-60 meq of elemental potassium, in 1000ml Normal saline, to run every 6-8 hours.
  - ✓ Use non dextrose containing fluids
  - ✓ Maximum concentration of potassium is 60meq in one liter of fluid.
  - ✓ Maximum rate of infusion (in the presence of perfuser machine) is 10meq/hour
  - ✓ Recommended if neuromuscular symptoms, cardiac arrhythmias, ongoing GI loss or severe hypokalemia
  - ✓ KCL 15-20 mEq/L in NS via peripheral vein. If > 40meq/L Kcl required, central vein needed

PLUS

- Potassium chloride **(KCl) tablet**, 600mg (equivalent to 8meq of potassium), 2-3tabs, PO, TID to QID.

Mild to moderate hypokalemia

- Potassium chloride **(KCl) tablet**, 600mg (equivalent to 8meq of potassium), 2-3tabs, PO, TID to QID.
- Potassium citrate, Potassium gluconate → Use in acidotic patient
- For Hypokalemia due chronic loop diuretics: Spironolactone-see doses in each indication (Heart Failure, liver cirrhosis)

Treatment of the cause

- Some causes of hypokalemia may be treated pharmacologically. See the examples below.
  - ✓ Vomiting - anti-emetics
  - ✓ Hypomagnesemia - magnesium sulfate
  - ✓ Hyperaldosteronism (Aldosteronism) — spironolactone
  - ✓ Potassium wasting tubulopathies - spironolactone or NSAIDS.
- Patients with chronic hypokalemia, the cause of which is not established need to be evaluated by nephrologist.

2) Hyperkalemia

- Hyperkalemia is defined as a serum potassium level of > 5.5mmol/l.
- It is considered **severe** if the serum potassium **is >6.5 mmo/l** or there is **ECG or clinical manifestation associated with the hyperkalemia.**

Potassium	Value (in mmol/L or meq/l)
Normal	3.5 - 5.0
Mild hyperkalemia	5.5 - 6.0
Moderate hyperkalemia	6 - 6.5
severe hyperkalemia	> 6.5

- ### Causes of hyperkalemia
  - I) **Low renal excretion**: AKI or CKD, spironolactone, ACE inhibitors/ARBS, NASAIDS, adrenal insufficiency
    *** A decrease in renal K+ excretion due to AKI or CKD is the most common underlying cause.**
  - II) **Excess intake:** potassium tablets, potassium rich diet in patients with AKI/CKD
  - III) **Release from intracellular space**: tumor lysis, rhabdomyolysis, hemolysis

IV) **Shift from intracellular space**: acidosis, digoxin, adrenergic blockers

V) **Pseudo hyperkalemia** (In-vitro cell death): tight tourniquet, thrombocytosis, erythrocytosis, marked leukocytosis

Clinical features

- Mild hyperkalemia is generally asymptomatic
- Severe hyperkalemia results in muscle weakness or paralysis, Dyspnea, Chest pain, palpitation or syncope, cardiac conduction abnormalities and cardiac arrhythmias.

Investigations and diagnosis

Diagnosis

- The diagnosis is made based of serum potassium determination.
- If there is no obvious cause, pseudo hyperkalemia needs to be excluded
- ECG is needed to assess the severity. *Refer short case of nitsibin for ECG features of Hyperkalemia (click here →* Electrolyte abnormalit *)*

Investigations

- RBS
- Serum potassium
- Serum creatinine and urea
- ECG
- Investigations for causes e.g. if adrenal insufficiency is suspected basal serum cortisol level will be needed for screening purpose.

Treatment

Non pharmacologic treatment

- Decrease food rich in potassium → see section on hypokalemia
- Discontinue medicines which increase potassium→ ACE- I, ARBs, Spironolactone, NSAIDs
- Dialysis: in refractory hyperkalemia due to AKI or CKD/ESRD

Pharmacologic treatment principles (For moderate to severe hyperkalemia)

✓ Mild hyperkalemia may actually protect against tachyarrhythmias.

- **Calcium gluconate,** 10ml of a 10% solution, IV, over 2-3 minutes, with constant cardiac monitoring. The dose can be repeated after 5 minutes, if the ECG changes of hyperkalemia persist or recur PLUS

- **Regular Insulin**, 10 units IV, followed immediately by 60-80ml ml of 40% dextrose (25g of glucose), every 4-6 hours) PLUS
- **Furosemide, 40 - 120mg**, IV, dose should depend on previous response, degree of kidney function impairment. The dose can be repeated according to response. PLUS
- **Salbutamol**, 10 to 20mg in 4 mL of saline by nebulization over 10 minutes or MDI (100µg/puff), 8 - 10 puffs every 20-30 minutes.
- **Sodium bicarbonate**, 1- 2mEq/kg, IV, bolus over 1-2 min; repeat as needed to improve cardiotoxic manifestations

Patients in whom the cause of potassium disorder is not clear need to be evaluated by nephrologist.

Treatment based on clinical feature and underlying cause

- shift potassium intracellularly.
  - ✓ Insulin + glucose. (10Iu RI + 50ml of 50% dextrose)
  - ✓ IV sodium bicarbonate:1-3 amps (44mEq per amp) IV over 20-30 min
  - ✓ Inhaled albuterol: 10-20mg nebulized over 10 min
- K+ > 6.0 without ECG Change → Enhance excretion of potassium with
  - ✓ Calcium or sodium polystyrene sulfonate (Kayexalate, 0.5 g/kg po (0.3—0.6 g/kg PO) in 2 mL/kg 70% sorbitol
  - ✓ Diuretics
- Hyperkalemia with EKG Changes, or cardiac arrest
  - ✓ Antagonize potassium-mediated Cardiotoxicity with Ca-gluconate, $CaCl_2$ or $NaHCO_3$
- Renal failure:
  - ✓ Hemodialysis effective at removing potassium
  - ✓ Furosemide: Effective in absence of oliguric renal failure, Causes potassium-losing diuresis
- Mineralocorticoid deficiency:
  - ✓ Hydrocortisone, fludrocortisones
- **Treat the underlying cause**

3) Hyponatremia

- **Normal serum sodium level is** 135 - 145 mmol/L
- Hyponatremia is defined as a plasma sodium concentration of < 135mmol/L.

- **Severe hyponatremia** is defined as a plasma sodium concentration of **<115 mmol/L**
- **Acute hyponatremia** is development of hyponatremia in **< 48 hours**
- **Chronic hyponatremia if duration known to be >48 hrs**
- Hyponatremia can be **due to a loss of sodium in excess of water, a gain of water in excess of sodium or both. Hyponatremia is a water problem, not a Na$^+$ problem. i.e. water intake > water excretion**
- **Causes of hyponatremia →** classified based on the volume status of the patient
  - ✓ **Hypovolemic hyponatremia** → diarrhea, vomiting, burn, polyuria
  - ✓ **Euvolemic hyponatremia** → syndrome of inappropriate ADH secretion (SIADH), hypothyroidism, low dietary solute intake
  - ✓ **Hypervolemic hyponatremia** → CHF, CKD, CLD, nephrotic syndrome.

Clinical features

- The symptoms directly attributable to hyponatremia primarily occur with acute and marked reductions in the serum sodium concentration and reflect neurologic dysfunction induced by **cerebral edema**, and possibly adaptive responses of brain cells to osmotic swelling. In this setting, the associated fall in serum osmolality creates an osmolal gradient that favors **water movement into the cells, leading to brain edema.**
- **Acute hyponatremia (duration known to be <48 hr.)**
  - ✓ Early: nausea, malaise, headache, muscle twitching, lethargy
  - ✓ Late/Severe: obtundation Confusion and disorientation, seizures, coma, Respiratory distress or arrest
- **Chronic hyponatremia (duration known to be >48 hr.)**
  - ✓ Frequently mild or no symptoms

Investigations and diagnosis

Diagnosis

- The diagnosis of hyponatremia is made based on the serum sodium level.
- Clinical evaluation is needed to classify the volume status of the patient and the more specific cause.

Investigation

- RBS
- Serum electrolytes
- Creatinine and BUN
- Serum osmolality to R/o pseudohyponatremia

  - ✓ Plasma osmolality = (2 x plasma Na^+) + $\frac{Glucose}{18}$ + $\frac{BUN}{2.8}$
  - ✓ Patients with hyponatremia have low osmolality (<275mosm/kg)
- ➢ CXR → If pulmonary pathologies (pneumonia, lung cancer) suspected.
- ➢ Urine Na
- ➢ Urine osmolality
- ➢ TFT → In euvolemic hyponatremia
- ➢ Serum cortisol → basal or random (in critical patients)
- ➢ Investigation directed to the suspected underlying cause

Treatment

Non pharmacologic treatment

- ➢ Free water restriction — for euvolemic and hypervolemic causes
- ➢ Encourage table salt intake-if not hypervolemic
- ➢ Discontinue thiazide diuretics
- ➢ Management of the underlying cause

Pharmacologic treatment

- ➢ Hypovolemic hyponatremia
  - ✓ **Normal saline**, IV infusion-volume depending on the estimated fluid deficit
- ➢ Hypervolemia hyponatremia
  - ✓ **Furosemid**e, dose depending on the underlying disease and previous response.
- ➢ Euvolemic hyponatremia: if it is severe/symptomatic acute hyponatremia
  - ✓ **3% NaCl** (513mmol of Na/L), IV, 1-2 ml/kg/hour
  - ✓ Should elevate the serum Na approximately 1-2mmol per hour
  - ✓ Raising the serum Na 4-6mmol/L over 2-3 hours is enough to prevent serious neurologic complications
  - ✓ Subsequently, the rate of correction should be less than 10mmol/L per 24 hours.

- ➢ As hypertonic saline is not commonly available, some practitioners advise patients to take more salt or an arbitrary amount of salt. This practice could be dangerous as it might result in overcorrection.
- ➢ The following could serve as an improvised guidance on preparing 3% NaCl oral solution
  - ✓ 1 tea spoon (tsp) of table salt = 6 g salt ≈ 2,400 mg sodium = 104 mmol sodium
  - ✓ A 500ml of standard 3% saline (3% hypertonic saline) contains 256.5mmol of sodium

- ✓ **To prepare as 500ml of 3% sodium chloride solution, add 2 and a ½ tsp (tea spoon of salt in 500ml of water.**
- ✓ **Example of administration**: For a 70kg male adult with an aim to increase serum sodium by 8mmmol/24 hour, give 35ml of the about solution every hour. (This should be given by measuring the amount using a syringe)

4) Hypernatremia

- ➢ Hypernatremia is defined as plasma sodium concentration of **>145mmol/l.**
- ➢ **Severe hypernatremia** is plasma sodium value of **>160 mmol/L.**
- ➢ Hypernatremia can be **due to loss of water, gain of sodium, or both. Loss of water is the more common denominator.**
- ➢ Individuals who can get and take water are unlikely to develop hypernatremia. Hence, the majority of patients who develop severe hypernatremia are patients who cannot get water by themselves e.g. patients with depressed mental status, stroke, on mechanical ventilator, the very elderly…

Causes of hypernatremia

- ➢ **Hypovolemic hypernatremia**
    - ✓ Renal water loss
        - ▪ Loop diuretics
        - ▪ post obstructive dieresis
        - ▪ osmotic diuresis → glucosuria
        - ▪ Hypercalcemia
        - ▪ Hypokalemia
        - ▪ Drugs like lithium
    - ✓ Extra renal water loss:
        - ▪ Burns
        - ▪ GI Losses → Diarrhea, vomiting, etc.
        - ▪ Insensible Loss (skin or lungs)
            - • Fever
            - • Hot Room
            - • Hyperventilation
                - o *In association with deficit in water intake (coma, stroke, immobility)*
                - o Small volume hyperosmolar > 600mosm urine: insensible loss
- ➢ **Euvolemic hypernatremia:** Diabetes insipidus, hypodipsia

- **Hypervolemic hypernatremia:** Iatrogenic (sodium bicarbonate, hypertonic saline), Salt poisoning in infants, Sea water ingestion

Clinical features

- Hypernatremia is basically a mirror image of hyponatremia. A rise in the serum sodium concentration and osmolality **causes water movement out of the brain** which **leads to shrinkage of brain cell volume** and secondary neurological symptom
- Mild and chronic hypernatremia is usually asymptomatic
- If conscious most patients with hypernatremia will have excessive thirst
- Severe acute hypernatremia causes CNS symptoms-irritability, lethargy, seizure and coma.

Manifestations of acute hypernatremia

- With acute hypernatremia defined as hypernatremia developing within hours, the rapid decrease in brain volume can cause rupture of the cerebral veins, leading to **focal ICH and SAH and possibly irreversible neurologic damage**.
- Acute hypernatremia can also result in demyelinating brain lesions similar to those associated with overly rapid correction of chronic hyponatremia.
- **The clinical manifestations of acute hypernatremia begin with lethargy, weakness, and irritability, and can progress to twitching, seizures, and coma.**
- **Severe symptoms** usually require an acute elevation in the serum sodium concentration to above **158 mEq/L.**
- Values above 180 mEq/L are associated with a high mortality rate, particularly in adults

Manifestations of chronic hypernatremia

- Chronic hypernatremia, which is **defined as hypernatremia that has been present for more than a day,** is much less likely to induce neurologic symptoms.
- Assessment of symptoms attributable to hypernatremia is often difficult because most affected adults have underlying neurologic disease. The latter is required to diminish the protective thirst mechanism that normally prevents the development of hypernatremia, even in patients with diabetes insipidus.
- Like hyponatremia, hypernatremia, even if mild, is associated with increased morbidity and mortality.

Investigations and diagnosis

Diagnosis

- Diagnosis is made based on serum sodium determination

Investigation

- Serum electrolytes

- Creatinine and BUN
- Urine specific gravity/osmolality
- Blood sugar
- If diabetes insipidus is suspected refer to next level of care after management of the acute state.

Treatment

Non pharmacologic treatment

- Avoid rapid correction.
- Encourage free water intake for thirst. This is the preferred route of correcting water deficit in conscious patients with intact thirst.

Pharmacologic treatment

- The main stay of treatment for hypernatremia is water (free water) given orally (preferred) or intravenously as 5%DW but the patients volume status depends on the severity of hypernatremia and the patient's volume state.
- **Hypovolemic Hypernatremia:**
  - ✓ **Ringer's lactate, IV,** until hypovolemia improves.
  - ✓ Once the hypovolemia improves **shift the fluid to 5%DW after calculating the water deficit.**
- **Euvolemic Hypernatremia:**
  - ✓ Correct water deficit using either **oral free water or 5%DW**
  - ✓ Replace ongoing losses
  - ✓ Consult specialist if Diabetes Insipidus is suspected.
- **Hypervolemic Hypernatremia:**
  - ✓ Thiazide diuretics are preferred if the volume overload is mild

  Alternative
  - ✓ Furosemide IV or P.O., dose and route depending on severity of hypervolemia.

Rate of correction of hypernatremia

- In acute hypernatremia (developing within hours) immediate reduction of serum Na is recommended but at a rate not exceeding **0.5mmol/hour over 48-72 hours**
- Correction should not exceed **10mmol/day.**
- Correction of chronic hypernatremia must occur slowly to prevent rapid fluid movement into the brain and cerebral edema, changes that can lead to seizures and coma

Calculation of water deficit

- **Water deficit = CBW x** $\left\lfloor \frac{serum\ Na}{140} - 1 \right\rfloor$
- **CBW** refers to estimated **current body water**
- CBW = 60% and 50% of body weight in younger men and women, respectively
- CBW= 50% and 45% in elderly men and women, respectively.

Patients suspected of having diabetes insipidus (with polyuria, polydipsia, dilute urine and no diabetes mellitus) should be evaluated by endocrinologist or internist.

5) Hypocalcemia

- Normal serum calcium level is 8.7 - 10.2 mg/dL (2.2 - 2.6 mmol/L) and ionized serum calcium level is 4.5 - 5.3 mg/dL (1.12 - 1.32 mmol/L)
- Total calcium should always be corrected for serum albumin.
- Corrected calcium = measured calcium + [0.8 x (4.0- serum albumin)]
- Hypocalcemia is defined as a corrected **total serum calcium level < 8.5 mg/dl** (<2.12 mmol/l) or **ionized serum calcium level < 4.5** mg/dL (<1.13mmol/l)
- Hypocalcemia is a common problem in clinical practice, both in ambulatory care and in hospitalized patients. More than 80% critically ill patients develop hypocalcemia.
- The major factors that influence serum calcium concentration are parathyroid hormone (PTH), vitamin D activity and their action on the kidneys and the intestine.
- Hypocalcemia is mainly caused by disorders related the level or activity of parathyroid hormone and/or vitamin D.
- The clinical presentation of hypocalcemia could vary from asymptomatic (incidental finding) to a life threatening one depending on the rapidity of development and severity.

Major causes of hypocalcemia

- **Hypocalcemia with inadequate PTH (low or inappropriately normal PTH)**
  - ✓ Surgical removal (commonly post thyroidectomy or parathyroidectomy)
  - ✓ Neck radiation

  - ✓ Autoimmune destruction
  - ✓ Idiopathic hyperparathyroidism

- ➢ **Hypocalcemia with high PTH**
  - ✓ CKD
  - ✓ PTH resistance: pseudohypoparathyroidism, hypomagnesemia
  - ✓ Vitamin D deficiency: Nutritional or malabsorption
  - ✓ Vitamin D resistant: Vitamin-D dependent or resistant rickets

- ➢ **Miscellaneous**
  - ✓ "Hungry bone syndrome" following parathyroidectomy
  - ✓ Extravascular deposition of calcium: hyperphosphatemia, pancreatitis, tumor lysis syndrome
  - ✓ Critical illness
  - ✓ Drugs: IV bisphosphonate therapy

Clinical features

- ➢ Chronic hypocalcemia is generally asymptomatic or cause mild symptoms.
- ➢ The hallmark of hypocalcemia is an irritable neuromuscular system which shows spontaneous or induced hyperexcitability, called tetany.
- ➢ Mild symptoms: perioral numbness, paresthesia of the hands and feet, muscle cramps, fatigue
- ➢ Severe clinical manifestations
  - ✓ **Tetany:**
    - ▪ Spams of hands and/or feet (**carpopedal spasm**): forced inward movement (adduction) of the thumb, flexion of metatarsophalangeal joints and wrists
    - ▪ Laryngeal spams: stridor or change in voice, air hunger
    - ▪ Induced tetany
      - **Trousseau's sign:** Carpal spasm induced but inflating sphygmomanometer 20mmHg above the systolic BP and keeping it for 3 minutes.
      - **Chvostek's sign**: elicited by tapping the facial nerve about 2cm in front of the ear (tragus) and observing contraction of the facial muscles. Chvostek's sign can also be seen in normal individuals. It has poor sensitivity and specificity.
  - ✓ **CNS manifestations**: Focal or generalized seizures, confusion, delirium, papilledema
  - ✓ **Cardiac manifestations:** hypotension, features of heart failure, prolonged QT on ECG

- ✓ **GI manifestations**; abdominal cramps, biliary colic
- ➢ Clinical features related to the underlying disease
  - ✓ Chronic hypoparathyroidism:
  - ✓ cataracts, poor dentition, dry skin, brittle nails, coarse hair, basal ganglia calcifications
  - ✓ Vitamin D deficiency in adults: diffuse bone pain and muscle weakness

Investigations and diagnosis

- ➢ ECG: look for prolonged QT interval
- ➢ If the cause of hypocalcemia is obvious e.g. post-thyroidectomy or post-parathyroidectomy, advanced chronic disease, or tumor lysis, further investigation might not be needed.
- ➢ The most important investigations need for identifying the possible cause of hypocalcemia are the following
  - ✓ Creatinine and BUN
  - ✓ Serum magnesium and phosphorus
  - ✓ Serum PTH (preferably intact PTH)
  - ✓ vitamin D level (25(OH)vitamin D)

Treatment

Non-pharmacologic

- ➢ Increase diet rich in calcium and vitamin D.

Pharmacologic

- ➢ **Hypocalcemia with severe symptoms** (tetany, seizure, change in mental status, prolonged QT) or acute (postoperative) <7.5mg/dl: IV calcium
- ➢ **Calcium gluconate (10%) 01 ampoule (10ml**) IV over at least 10min (rule of 10)
  - ✓ If symptoms persist, repeat the above. Don't repeat more than two times.
  - ✓ Give a continuous infusion (drip) of calcium in the following way
    - ▪ Add 06 ampoules of 10% calcium gluconate in 1L of 5%DW run 12 hours (80ml/hr or 28 drops/minute).
    - ▪ This equivalent to 540mg of elemental calcium in 1000ml = 0.54mg/ml preparation running at about 45mg/hour)
  - ✓ Do serum calcium every 12 hour and continue infusion until calcium reaches 8mg/dl

- ✓ Start oral calcium (see below) as soon as the patient is able to take orally, overlap with the intravenous infusion.

- ➢ **Severe hypocalcemia in the presence of hypomagnesemia**: correct the magnesium first
  - ✓ IV magnesium sulfate: see hypomagnesemia treatment
  - ✓ Give also calcium gluconate as above.
- ➢ **Long-term calcium replacement therapy**: for mild hypocalcemia and after IV calcium in sever hypocalcemia.
  - ✓ Give elemental calcium 1500 to 2000mg/day, BID or TID
    - ▪ **Calcium carbonate 1000mg** (equivalent to 400mg elemental calcium), 2tabs, PO, BID or TID
  - ✓ Target serum calcium is to keep it between 8-9mg/dl. Don't go beyond 9mg/dl.
- ➢ **Vitamin D supplementation or correction of deficiency** (if confirmed)
  - ✓ Vitamin D3 or D2: If deficiency confirmed (50,000IU weekly for 6-8weeks), if not yet confirmed, give 800IU/day empirically.

6) Hypercalcemia

- ➢ Hypercalcemia is defined as a total serum calcium >10.3mg/dl or an ionized calcium >5.2mg/dl (2.6mmol/l)

Hypercalcemia	total serum calcium level (in mg/dl)
Mild	10.3 - 12
Moderate	12 -14
Severe	>14

- ➢ The most important denominator in the causation of hypercalcemia is increased bone resorption. The contribution of increased oral absorption is modest.
- ➢ **The two most common causes of hypercalcemia are primary hyperparathyroidism and malignancy accounting 90 % of cases.**
- ➢ The work up of hypercalcemia is focused on differentiating the two (primary hyperparathyroidism and malignancy)
- ➢ Other less common causes include
  - ✓ Increased vitamin D activity: excess ingestion, overproduction in granulomatous diseases (tuberculosis, sarcoidosis)
  - ✓ Decreased renal excretion: Familial hypocalciuric hypercalcemia
  - ✓ Tertiary hyperparathyroidism: in advanced CKD
  - ✓ Endocrinopathies: hyperthyroidism, adrenal insufficiency

  - ✓ Drugs: thiazide diuretics, Lithium
  - ✓ Excess calcium intake

Clinical features

- Mild hypercalcemia is generally asymptomatic
- Symptom develop if severe hypercalcemia develops over a shorter period of time
- Symptoms are remembered as **"Stones, bones, moans and groans".**
- Bone pain
- Fatigue, muscle weakness
- Polyuria, polydipsia, kidney stones
- Constipation, anorexia, nausea, vomiting, constipation, pancreatitis
- High blood pressure
- Anxiety, depression, cognitive dysfunction
- Confusion and coma

Investigation and diagnosis

Diagnosis

- Once hypercalcemia is confirmed from serum total calcium or ionized calcium, the next step important investigation is determination of serum PTH.
- Low PTH: very likely hypercalcemia due to malignancy or vitamin D related causes
- High or normal PTH: Hyperparathyroidism
- If serum PTH can't be done and the patient has overt malignancy, consider the hypercalcemia to be due to the malignancy.

Investigations

- Other investigation for patients with low serum PTH
  - ✓ Investigate for malignancy based on clinical clues e.g. screening for multiple myeloma
  - ✓ Serum 25(OH) and 1,25(OH)Vitamin D
- **Phosphorous:** low in primary hyperparathyroidism, elevated in Vitamin D related causes
- ECG: short QT interval
- **X-rays:** osteoporotic changes in cortical bone, typically in the wrist, bone cysts (osteitis cystica fibrosa) in the long bones
- **Ultrasound:** Renal stones or evidence of nephrolithiasis

Treatment

Non-pharmacologic treatment

- If the patient has severe hypercalcemia (>14mg/dl) or has severe symptoms (features of dehydration, change mental status) urgent admission is needed.
- Discontinue drugs which can cause hypercalcemia: thiazide, lithium
- Surgical management: in primary hyperparathyroidism, if there are indications.
- Management at referral hospital level is strongly recommended.

Pharmacologic treatment

Severe hypercalcemia

- **Aggressive hydration with normal saline** for few days
  - ✓ **4-6 liters of NS over 24 hours** (1 liter over 4-6 hours), close monitoring for fluid overload and fluid balance.
  - ✓ Do not routinely use Furosemide unless the patient is fluid overloaded (pulmonary crackles, raised JVP).
  - ✓ If Fluid overloaded, Furosemide, 20-40mg IV, when needed. Similar doses of can be repeated if fluid overload persists.
- **Intravenous bisphosphonate**
  - ✓ **Zoledronic acid, 4mg,** diluted in 100ml of NS or D5W, given as infusion over 15-30minutes.
- **Corticosteroids**
  - ✓ Dexamethasone 4mg IV BID OR
  - ✓ Hydrocortisone 100mg IV, BID OR
  - ✓ Prednisolone 30-40mg/day.

7) Hypomagnesemia

- The major dietary sources of magnesium are green vegetables (such as spinach), nuts and whole grains (cereals).
- Units of serum magnesium measurement and normal values:
  - ✓ Serum magnesium can be reported in any of the three units: **mmol/l, mEq/l or mg/dl.**
  - ✓ The molecular weight of magnesium is **24.3** and its valence is **2 (+2).** Hence. the relationship between the units is as follows

- mEq/l = mmol/L x 2 OR mmol/l= mEq/l ÷ 2

- mg/dl = 2.43 x mmol/l OR mg/dl= 1.21 x mEq/l

- The normal range for serum magnesium is **1.7 to 2.1 mg/dl**= 1.4 to 1.7 mEq/l= 0.70 to 0.85 mmol/L.
- **Hypomagnesemia** is defined as serum magnesium **<1.6mg/dl** or < 0.66 mmol/L (<1.3mEq/L).

Hypomagnesemia	serum magnesium level (in mg/dl)
Mild	1.2 - 1.6
Moderate	1.2 - 1.5
severe	<1.2

- **Clinically significant symptoms and signs** do not commonly occur until the level falls **below 1.2 mg/dL.**
- Hypomagnesemia is common in hospitalized patients, particularly critically ill patients.
- The mechanisms of hypomagnesemia development are renal losses, GI losses or poor intake, redistribution (shift or sequestration) or a combination.

Table. Causes of hypomagnesemia

Mechanisms	Causes
Renal loss	➢ Medications ✓ Loop or thiazide diuretics (Not potassium sparing diuretics) ✓ Nephrotoxic medications: aminoglycosides, amphotericin B, Cisplatin and Cyclosporine ➢ Polyureic states ✓ Postobstructive diuresis ✓ polyureic phase of recovering AKI (ATN) ✓ DKA ➢ Extracellular fluid expansion (hyperfiltration) ✓ Aggressive saline infusion ➢ Hypercalcemia ➢ Inherited renal tubular disorders: Gitelman or Barrter syndrome

Gastrointestinal causes	➢ Diarrhea ➢ Prolonged NG tube suction or prolonged vomiting ➢ Prolonged PPI use ➢ Malabsorption ➢ Small bowel resection ➢ Severe malnutrition ➢ Chronic alcohol dependence
Redistribution (shifting in to the intracellular space) or sequestration	➢ Correction of DKA ➢ Refeeding syndrome ➢ Hungry bone syndrome: after parathyroidectomy or thyroidectomy ➢ Acute pancreatitis

Clinical features

- **Asymptotic**: Mild hypomagnesemia developing slowly is usually asymptomatic.
- **Symptomatic:** The major manifestations are neuromuscular, cardiovascular, and refractory electrolyte abnormalities.
- **Neuromuscular: Neuromuscular hyperexcitability**
  - ✓ Positive Chvostek's and Trousseau's signs
  - ✓ Tetany
  - ✓ Tremor, fasciculation
  - ✓ Seizure
  - ✓ Confusion
- **Cardiovascular: ECG abnormalities or life-threatening ventricular arrhythmias**
  - ✓ Early ECG abnormalities: Wide QRS, peaked T-wave
  - ✓ Late ECG abnormalities: Progressive widening of QRS, prolonged PR interval and diminished T-wave
  - ✓ Arrhythmias: Torsade's de pointes, a repetitive polymorphic ventricular tachycardia with QT prolongation
  - ✓ Increase risk of digoxin toxicity
- **Electrolyte abnormalities**
  - ✓ Hypokalemia: refractory to potassium replacement alone
  - ✓ Hypocalcemia: refractory to calcium and vitamin D treatment alone
- **Normal serum magnesium with magnesium depletion**
  - ✓ Patients with refractory hypokalemia and hypocalcemia should be suspected to have magnesium depletion despite normal serum magnesium. This is particularly true for patients with risk factors (e.g. chronic diarrhea, alcohol abuse, long term diuretic use)

Diagnosis and investigation

Diagnosis

- **Whom to screen for hypomagnesemia?**
  - ✓ Critically ill patients admitted to ICU
  - ✓ All patients with hypokalemia or hypocalcemia
  - ✓ Patients with clinical manifestations suspicious of hypomagnesemia
  - ✓ Patients with potential causes for hypomagnesemia: chronic diuretic use, nephrotoxic medication, prolonged PPI use, polyuric patients, chronic diarrhea, alcohol dependence, post parathyroidectomy/thyroidectomy
- **Confirming hypomagnesemia:** serum magnesium level (watch the unit)
- **Identifying the cause of hypomagnesemia**
  - ✓ Hx of drug use, history of diarrhea, alcohol use, and nutritional assessment.
  - ✓ If the cause is not obvious determine 24hour urine magnesium. A 24hour urine magnesium excretion >10mg should be considered renal wasting and <10mg suggests GI loss or transcellular shift.

Investigation: additional investigations needed

- Serum potassium
- Serum calcium
- ECG
- Serum creatinine: To help decide the rate of treatment

Treatment

Non-pharmacologic treatment

- **Correction of the underlying cause**: e.g. discontinuation of diuretics, nephrotoxic medications, treating diarrhea, helping to decrease/quit alcohol.
- **Increase dietary intake of magnesium**: Food rich in magnesium: Green leafy vegetables, nuts or peanuts, legumes (e.g. beans), soy milk, and whole grains

Pharmacologic treatment

Treatment of severe (<1.2mg/dl) and symptomatic hypomagnesemia

- **Life threatening** (arrhythmia)
  - ✓ **IV Magnesium sulfate1- 2g,** IV push over 3-5 minutes, Followed by continuous infusion
- **Emergent**: No arrhythmia but severe symptoms (e.g. neuromuscular manifestations)
  - ✓ **IV Magnesium sulfate, 1 to 2g diluted in 100mL D5W**, run 15-30minutes, Followed by continuous infusion.
- **Non-emergent repletion** in patients with severe hypomagnesemia
  - ✓ Start with continuous infusion. Avoid the initial bolus.
  - ✓ **How to give continuous infusion?**

    - 4 - 6 g magnesium sulfate diluted in 1-2 liters of D5W to run over 12 to 24 hours. E.g. 3g magnesium sulfate in 1000ml D5W runs over 12 hours.
  - ✓ **Duration of continuous infusion**
    - Continuous infusion should continue for **two more additional days** after correction of the serum magnesium.

- ➢ **Patients with significantly impaired kidney function (eGFR<30ml/min):**
  - ✓ Because of the risk for severe hypermagnesemia, 50% of the magnesium sulfate dose described above should be given.
- ➢ **Monitoring serum magnesium**
  - ✓ Serum magnesium should be determined 1-2 times per day
- ➢ **Major adverse effect**
  - ✓ The major adverse effect of IV magnesium sulfate is iatrogenic hypermagnesemia, which almost exclusively occurs in patients with impaired kidney function.
  - ✓ **Monitor for depressed/absent DTR, bradycardia and low BP**, which are the major manifestations of hypermagnesemia.

Moderate hypomagnesemia (1.2- 1.5mg/dl) in inpatient setting

- ✓ IV magnesium sulfate 2gm in 1000ml D5W to run 12-24 hours.

Continue Potassium or Calcium infusions

- ➢ In patients with severe hypokalemia or hypocalcemia associated with hypomagnesemia, **IV infusions of potassium or calcium should be continued** as correction of magnesium takes long periods of time (a few to several days)

Oral magnesium

- ➢ Oral magnesium should be started along with or after IV magnesium sulfate.
- ➢ Most oral magnesium preparations are poorly absorbed and poorly tolerated (due to diarrhea)
- ➢ 240 - 1000mg of elemental magnesium is needed in 24 hours.
- ➢ The most commonly available oral magnesium preparation available is magnesium hydroxide.
  - ✓ **Magnesium hydroxide (liquid form),** 400mg/5ml (168mg elemental Mg5ml) give 10ml BID-TID.
  - ✓ If it is combined with Aluminum, avoid prolonged use.

Pharmacologic treatment of renal potassium loss (wastage):

- ➢ Potassium sparing diuretics also spare magnesium.
- ➢ In situations where is continued renal loss of magnesium, give magnesium alone fails to correct the hypomagnesemia.

- These situations include: continued need to use **diuretics, nephrotoxic medications** until tubular injury recovers (Cisplatin, Amphotericin B, Aminoglycosides), **inherited tubulopathies** (Gitelman or Barrter syndrome).
- **Spironolactone** starting dose 25-50mg/day or 2 divided doses, maximum 400mg/day or in two divided doses

8) Hypermagnesemia

- Hypermagnesemia is defined as a serum magnesium level **> 2.5mg/dL** (>1.1mmo/L or > 2.2mEq/L). However clinical symptoms do not generally occur unless serum magnesium is **>5mg/dL**
- Hypermagnesemia is relatively uncommon in clinical practice and symptomatic hypomagnesemia is much less common. This is due to the kidney's tremendous capacity to excrete excess body magnesium.
- Hypermagnesemia occurs in three clinical settings
  - ✓ **Marked impairment in kidney function** (acute or chronic)
  - ✓ **Iatrogenic or accidental excess infusion or ingestion** of magnesium: typically, in the setting of treatment for preeclampsia or eclampsia with IV magnesium sulfate
  - ✓ **Excess release from the intracellular compartment** (generally with impaired kidney function): Tumor lysis syndrome, rhabdomyolysis.

Clinical features

- **Asymptomatic**: serum magnesium level **2.5 -5mg/dL**, though defined as hypermagnesemia, is generally asymptomatic unless there is a concomitant hypocalcemia.
- **Symptomatic**: The major symptoms and signs of hypermagnesemia are related to neuromuscular or cardiovascular system.
- **Neuromuscular:** characterized by depressed neuromuscular conduction(activity)
  - ✓ **Mild:** Nausea, vomiting, constipation, facial flushing, dizziness, depressed deep tendon reflexes.
  - ✓ **Moderate:** Absent deep tendon reflexes, drowsiness, paralytic ileus, urinary retention, blurred vision, and hypotension.
  - ✓ **Severe (life threatening):** flaccid paralysis, respiratory depression, coma, apnea.
- **Cardiovascular**: characterized by delayed(depressed) cardiac conduction
  - ✓ **ECG abnormalities (every conduction is delayed):** prolonged PR interval, AV block, prolonged QRS duration, prolonged QT interval.
  - ✓ **Severe (Life threatening):** bradycardia advanced AV-block, cardiac arrest/asystole.
  - ✓ **Hypocalcemia:** hypermagnesemia suppresses PTH secretion

Table. Correlation between serum magnesium level and clinical manifestations	
Serum magnesium level	**Symptoms/signs**
5-7mg/dl	Nausea, vomiting, constipation Facial flushing Dizziness
7-12mg/dl	Urinary retention, ileus, Blurred vision, confusion, lethargy Loss of deep tendon reflexes Prolonged PR interval, wide QRS, prolonged QT Hypotension
>12mg/dl	Flaccid paralysis Respiratory depression Coma Advanced AV-block/bradycardia Cardiac arrest

Diagnosis and investigations

- A serum magnesium level >2.5mg/dl confirms the presence of hypermagnesemia.
- **Additional important investigations** needed in those with confirmed hypermagnesemia
  - ✓ RFT: creatinine and Egfr
  - ✓ Serum calcium, phosphorous and potassium
  - ✓ ECG
- **Monitoring serum magnesium level**: patients receiving parenteral magnesium sulfate need baseline RFT, ECG, close follow up of serum magnesium, DTR and mental status.
- **Additional history**: history of excess magnesium ingestion (antacids or magnesium-based laxatives).

Treatment

Non-pharmacologic

- Stop magnesium infusion or oral magnesium containing drugs.
- Hemodialysis: In symptomatic hypermagnesemia with impaired kidney function

Pharmacologic

- **Symptomatic hypermagnesemia:**
  - ✓ **Intravenous calcium**
    - **Calcium gluconate 10%,** 10ml, diluted in 100ml D5W to run over 5-10 minutes.
    - In patients with cardiac arrest, give undiluted over 2-3 minutes.
    - Repeat the dose, if symptoms persist.

- ✓ **Forced diuresis**
    - **Normal saline 200ml/hour** for 6 -12 hours, if the patient does not have volume overload (edema, pulmonary congestion, and hepatomegaly).
    - Give **Furosemide 40mg, IV, stat**, in the middle of the NS infusion.

- ✓ **Hemodialysis**
    - In patients with significantly impaired kidney function (eGFR<30ml/min) and symptomatic hypermagnesemia, excretion of the magnesium is unlikely to happen; hence urgent hemodialysis is needed after giving.
- ➢ **Asymptomatic hypermagnesemia**
    - ✓ No need for pharmacologic treatment.
    - ✓ Stopping magnesium containing medications or magnesium sulfate infusion, if being given, will suffice.

Prevention

- ➢ During parenteral magnesium sulfate administration
    - ✓ Determine baseline serum creatinine and continuously monitor urine output
    - ✓ Monitor serum magnesium regularly every 6 hours
    - ✓ If possible, have ECG monitoring (bedside monitor)
- ➢ Avoid prolonged use of magnesium containing medications in patients with impaired kidney function medications (antacids or magnesium containing laxatives)

3.12.4 STI (የአባላዘር በሽታ)

- ➢ Sexually Transmitted infections (STI's) are serious and common problems worldwide.
- ➢ There are more than 20 types. Many of these are curable with effective treatment, but continue to be a major health problem for an individual and the community at large.
- ➢ With the emergence of HIV/AIDS the management of STIs makes more serious issue and calls for early screening, effective and urgent management.
- ➢ There are **two basic approaches in the management** of STIs namely **etiologic diagnosis** using laboratory tests and **syndromic approach.** Both classic approaches present with a number of problems.

1. **Etiologic diagnosis** approach is often regarded as the **ideal** way of diagnosing disease
2. **The syndromic approach** is the choice of resort when there are no laboratory facilities. The syndromic case management has the following

key features:

- It enables all trained first line health care providers to diagnose STI syndromes and treat patients on the spot, without waiting for laboratory results.
- It will help to offer treatment on the initial visit which is an important step to stop the spread of the disease.
- It is problem oriented (it responds to the patient's smx's).
- It is highly sensitive and does not miss mixed infections.
- Uses **flow charts** that guide the health worker through logical steps.
    - ✓ Each flowchart is made up of a series of steps:
        - The clinical problem- the patient's presenting symptoms at the top; this is the starting point
        - A decision to make, usually by answering "yes" or "no" to a question
        - An action to take: what you need to do
- Provides opportunity and time for education and counseling.

NB: A number of different organisms that cause STIs give rise to only a limited number of syndromes.

- The aim of syndromic STI management is to identify one of the 7 syndromes and manage accordingly. These are
    1) Vaginal discharge
    2) Urethral discharges
    3) genital ulcer
    4) lower abdominal pain
    5) scrotal swelling
    6) inguinal bubo
    7) neonatal conjunctivitis.

1) Vaginal Discharge Syndrome/VDS/

- Abnormal vaginal discharge in terms of quantity, color or odor could be most commonly as a result of vaginal infections.
- It is a poor indicator of cervicitis, especially in young girls because a large proportion of them are asymptomatic.

Etiology

- **Bacterial vaginosis** (Gardnerella vaginalis) is the leading cause of vaginal discharge in Ethiopia
- The following are most common causes of vaginal discharge listed based on decreasing order of frequency in Ethiopia

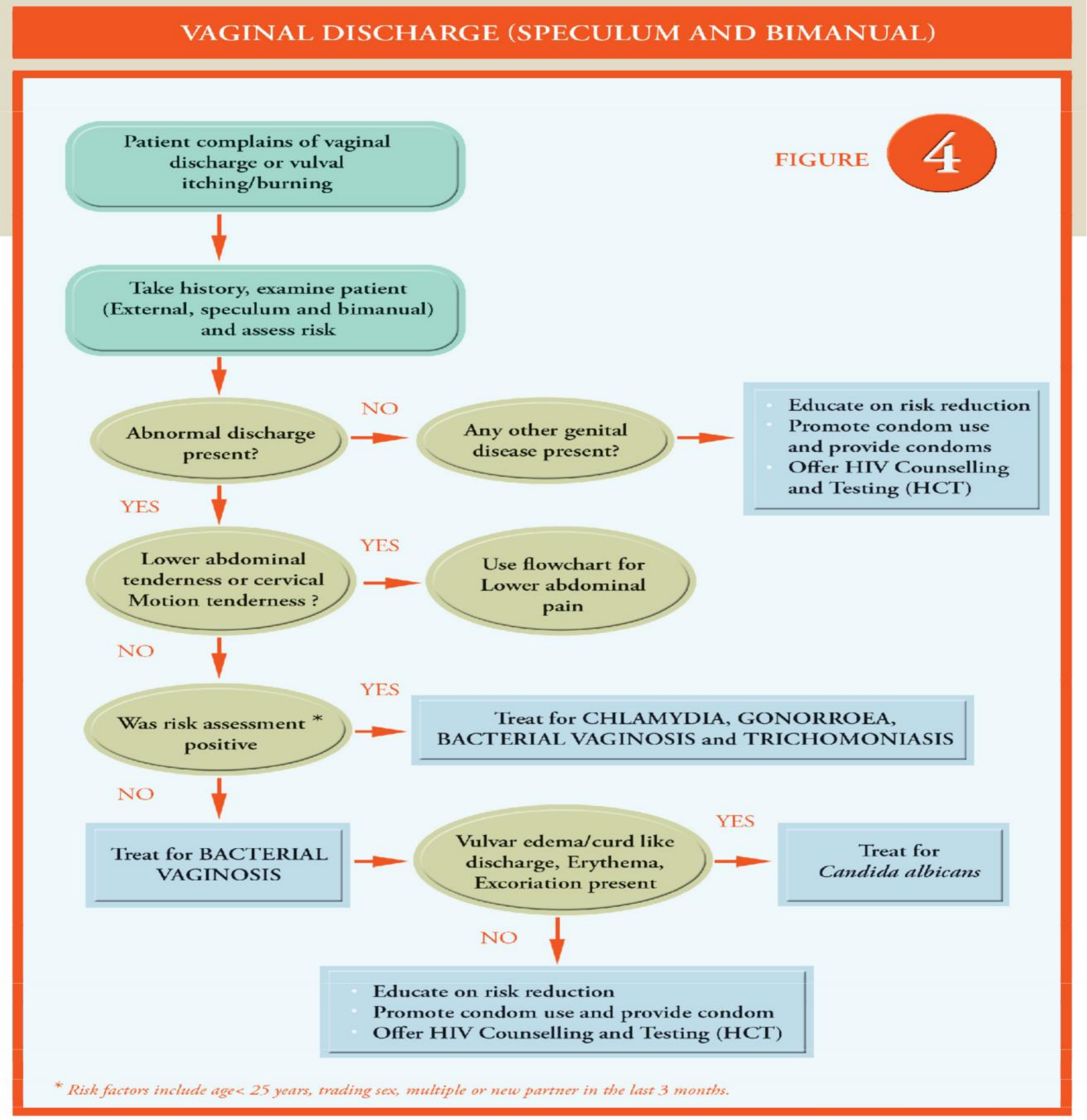
- ✓ Gardnerella vaginalis (Polymicrobial) } endogenous infections
- ✓ Candida albicans.
- ✓ Trichomonas vaginalis } sexually acquired
- ✓ Neisseria gonorrhoeae
- ✓ Chlamydia trachomatis

Risk Assessment

- ➢ Major risk factor for cervicitis using vaginal discharge as an entry point to manage cervical infection is far from ideal.
- ➢ While vaginal discharge is highly indicative of vaginal infection, it is poorly predictive of cervical infection with gonorrhea and/or chlamydia.
- ➢ The flowchart may become more predictive of cervical infection if a number of risk factors indicative of cervical infection are included
- ➢ *N.B. One or more of the following are risk factors for STI related cevicitis in Ethiopia*

- ✓ Multiple sexual partners in the last 3months.
- ✓ New sexual partner in the last 3 months
- ✓ Ever traded sex
- ✓ Age below 25 years

NB: The presences of one or more risk factor suggest cervicitis.


VAGINAL DISCHARGE (SPECULUM AND BIMANUAL)
FIGURE 4
Patient complains of vaginal discharge or vulval itching/burning
Take history, examine patient (External, speculum and bimanual) and assess risk
Abnormal discharge present?
NO
Any other genital disease present?
Educate on risk reduction
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
YES
Lower abdominal tenderness or cervical Motion tenderness ?
YES
Use flowchart for Lower abdominal pain
NO
Was risk assessment * positive
YES
Treat for CHLAMYDIA, GONORROEA, BACTERIAL VAGINOSIS and TRICHOMONIASIS
NO
Treat for BACTERIAL VAGINOSIS
Vulvar edema/curd like discharge, Erythema, Excoriation present
YES
Treat for Candida albicans
NO
Educate on risk reduction
Promote condom use and provide condom
Offer HIV Counselling and Testing (HCT)
* Risk factors include age< 25 years, trading sex, multiple or new partner in the last 3 months.

Figure; The algorithm of syndromic case management of vaginal discharge

Treatment

- Vaginal discharge syndrome can cause devastating complications if left untreated.
- Hence any woman with vaginal discharge syndrome must be treated promptly.
- Look at table below

2) Lower Abdominal Pain/Pelvic inflammatory disease/(PID)

- All sexually active women presenting with lower abdominal pain should be carefully evaluated for the presence of upper genital tract infections (tube, uterus, ovaries, and pelvic cavity).
- In addition, all women with presumptive STI should undergo thorough bimanual and abdominal examination because some of the women with PID may not complain of lower abdominal pain.
- Other **suggestive symptoms** include **pain during intercourse, vaginal discharge, abnormal vaginal bleeding (inter-menstrual), painful urination, pain during menstruation, fever and sometimes nausea and vomiting.**
- PID is difficult to diagnose because the clinical manifestations widely vary.
- PID becomes highly probable when one or more of the above symptoms are seen in a woman with adnexal tenderness, vaginal discharge and cervical motion tenderness.

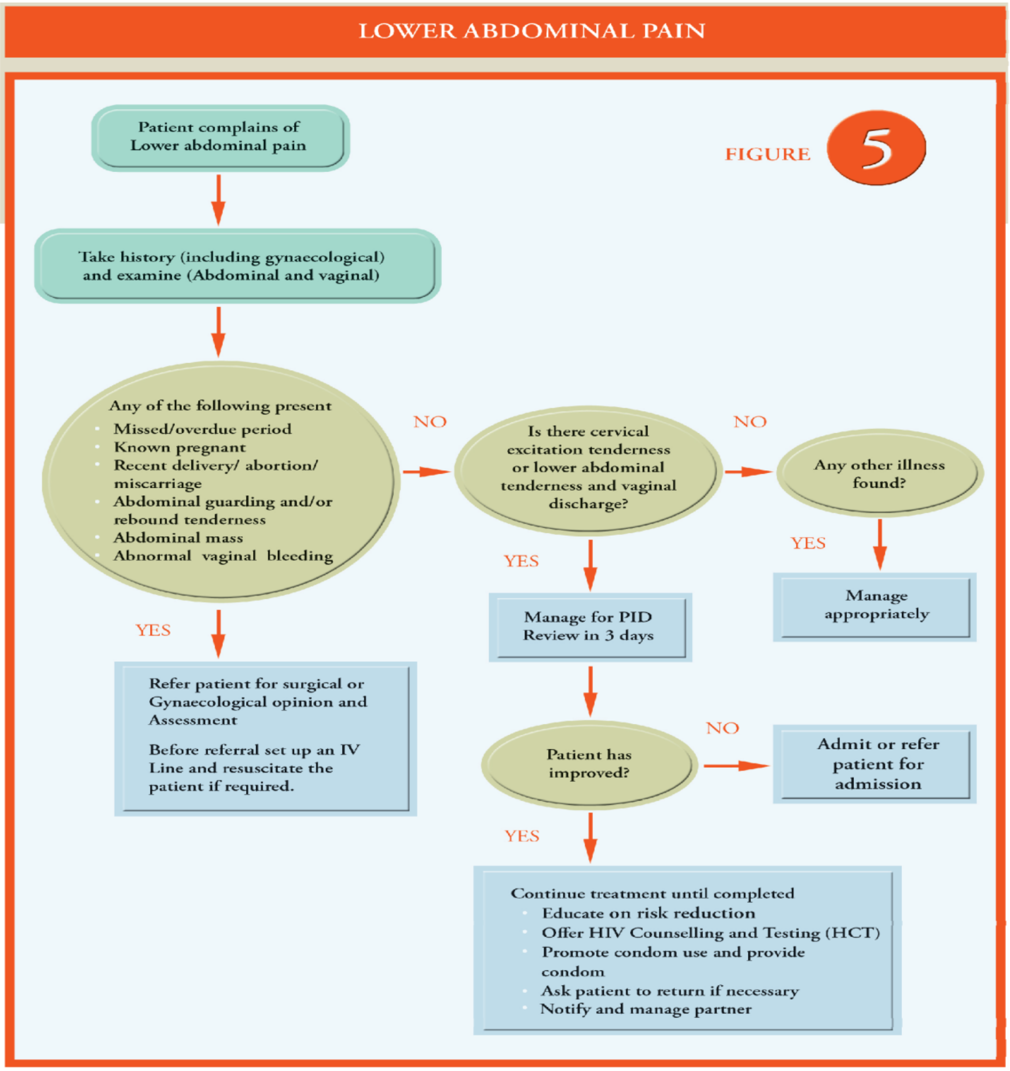
Indications for hospital admission with acute PID

- The diagnosis is uncertain
- Surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded
- A pelvic mass is suspected
- Severe illness precludes management on an outpatient basis
- PID in pregnancy
- The patient is unable to follow or tolerate an outpatient regimen
- Failed to respond to outpatient treatment

N.B. Many experts recommend that all patients with PID should be admitted to hospital for treatment.

Etiology

- The most common causative agents responsible for this syndrome include **N.gonorrhae, C.trachomatis, and anaerobic bacteria.**
- Facultative Gram-negative rods and Mycoplasma hominis are also implicated sometimes.
- As it is difficult to differentiate between these clinically, and a precise microbiological diagnosis is nearly impossible in most clinical set ups, hence the treatment regimen must be effective against the incriminated microorganisms.


LOWER ABDOMINAL PAIN
FIGURE 5
Patient complains of Lower abdominal pain
Take history (including gynaecological) and examine (Abdominal and vaginal)
Any of the following present
Missed/overdue period
Known pregnant
Recent delivery/ abortion/ miscarriage
Abdominal guarding and/or rebound tenderness
Abdominal mass
Abnormal vaginal bleeding
NO
Is there cervical excitation tenderness or lower abdominal tenderness and vaginal discharge?
NO
Any other illness found?
YES
Manage appropriately
YES
Manage for PID Review in 3 days
YES
Refer patient for surgical or Gynaecological opinion and Assessment
Before referral set up an IV Line and resuscitate the patient if required.
Patient has improved?
NO
Admit or refer patient for admission
YES
Continue treatment until completed
Educate on risk reduction
Offer HIV Counselling and Testing (HCT)
Promote condom use and provide condom
Ask patient to return if necessary
Notify and manage partner

Figure; The algorithm of syndromic case management of lower abdominal pain

Treatment

- **Look at table below**

3) Urethral Discharge Syndrome (UDS)

- Urethral discharge is the presence of abnormal secretions from the distal part of the urethra and it is the **characteristic manifestation of urethritis.**
- Urethritis is usually due to STI's although UTI may produce similar symptoms.
- Urethral discharge is **one of the commonest STI** among men in our country.

Cause or Etiology of UDS

- Urethral discharge can be caused by many different causative micro-organisms (either single or polymicrobial).
- The **two most common** causative agents of the syndrome are **Neisseria gonorrhea and Chlamydia trachomatis** (81% and 36.8% respectively).
- **Most of the time** urethral discharge is due to **mixed infection** of Neisseria gonorrhea and Chlamydia trachomatis
- Some of the other causative micro-organisms are mycoplasma genitalium, Trichomonas vaginalis, and Ureaplasma urealyticum.
- In some rare cases it can be also the result of non-infectious causes.
- Due to these reasons urethral discharge is a syndrome of many causes rather than a single disease to be dealt with and it needs to be dealt with as a syndrome while it is being managed.

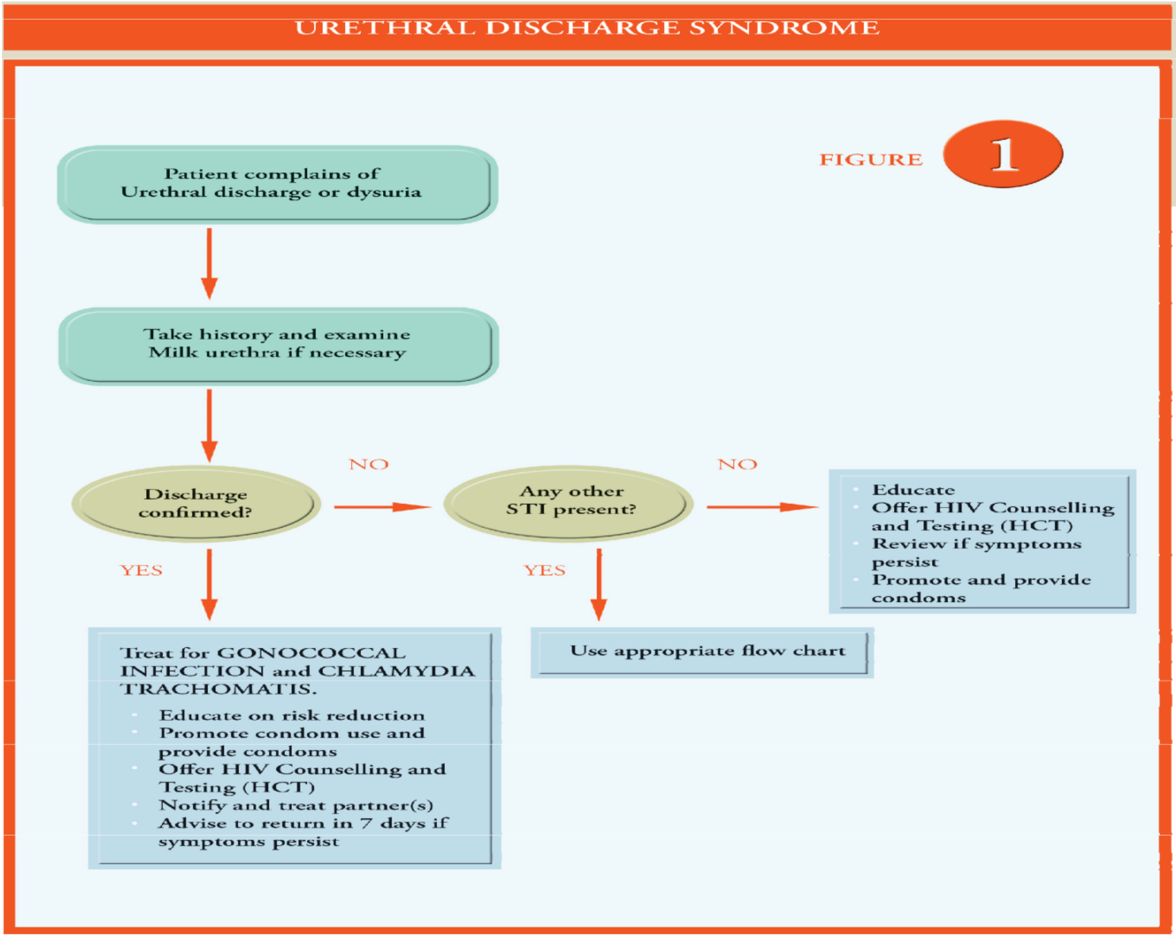
Clinical manifestations of UDS

- The common signs and symptoms of UDS are
  - ✓ Burning sensation (**dysuria**) during micturition
  - ✓ Increased **urgency and frequency** of urination
  - ✓ **Itching** sensation of the urethra.
- **Urethral discharge:**
  - ✓ The amount and nature of the discharge vary according to the causative agents and other factors like prior treatments with antibiotics.
  - ✓ The appearance of the discharge can be **purulent or mucoid, clear, white, or yellowish, green.**
  - ✓ Sometimes it can be associated with scrotal swelling and pain which tends to be unilateral.
  - ✓ The urethritis caused by N. gonorrhea has usually an acute onset with profuse and purulent discharge and the one caused by C. trachomatis has sub-acute onset with scant mucopurulent discharge.

Complications of UDS

- Common acute complications
  - ✓ Disseminated gonococci syndrome
  - ✓ Perihepatitis
  - ✓ Acute epididymoorchitis
- Common chronic complications
  - ✓ Urethral stricture
  - ✓ Infertility

- ✓ Reiter's syndrome (the most common type of inflammatory polyarthritis in young men)


URETHRAL DISCHARGE SYNDROME
FIGURE 1
Patient complains of Urethral discharge or dysuria
Take history and examine Milk urethra if necessary
Discharge confirmed?
NO
Any other STI present?
NO
Educate
Offer HIV Counselling and Testing (HCT)
Review if symptoms persist
Promote and provide condoms
YES
Treat for GONOCOCCAL INFECTION and CHLAMYDIA TRACHOMATIS.
Educate on risk reduction
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
Notify and treat partner(s)
Advise to return in 7 days if symptoms persist
YES
Use appropriate flow chart

Figure; The algorithm of syndromic case management of urethral discharge syndrome

Treatment of UDS

- ➢ UDS needs to be treated ASAP because if it is not treated on time it can cause serious complication.
- ➢ Treatment should target gonorrhea and chlamydial infections.
- ➢ Look at the table below

Persistent/Recurrent Urethral Discharge

- ➢ Some patients may complain of persistent or recurrent burning sensation or dysuria on urination, with or without discharge, due to various reasons.
  - ✓ Inadequate treatment or poor compliance and/or
  - ✓ Re-infection (partner/s not managed)
  - ✓ Persistent urethritis after Doxycycline based treatment might be caused by doxycycline resistant M. genitalium

- ✓ T. vaginalis is also known to cause Urethritis in men, hence the index patient should be treated for this.
- ✓ Infection by drug-resistant organisms (N. gonorrhea)

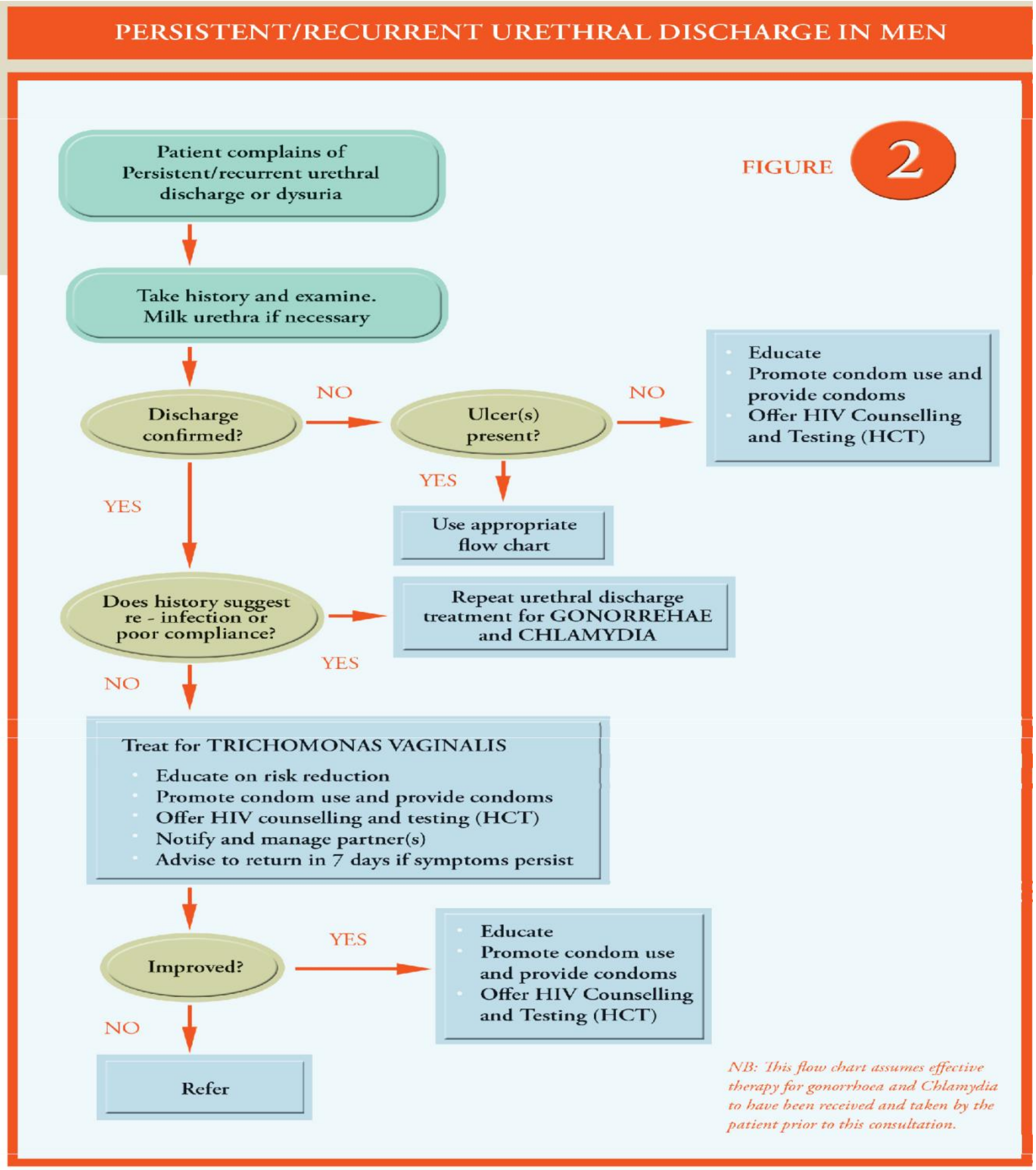

PERSISTENT/RECURRENT URETHRAL DISCHARGE IN MEN
FIGURE 2
Patient complains of Persistent/recurrent urethral discharge or dysuria
Take history and examine. Milk urethra if necessary
Discharge confirmed?
NO
Ulcer(s) present?
NO
Educate
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
YES
Use appropriate flow chart
YES
Does history suggest re - infection or poor compliance?
YES
Repeat urethral discharge treatment for GONORREHAE and CHLAMYDIA
NO
Treat for TRICHOMONAS VAGINALIS
Educate on risk reduction
Promote condom use and provide condoms
Offer HIV counselling and testing (HCT)
Notify and manage partner(s)
Advise to return in 7 days if symptoms persist
Improved?
YES
Educate
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
NO
Refer
NB: This flow chart assumes effective therapy for gonorrhoea and Chlamydia to have been received and taken by the patient prior to this consultation.

Figure: The algorithm of syndromic case management of persistent or recurrent urethral discharge syndrome in men

Treatment of Persistent/Recurrent Urethritis Syndrome

- ➢ Look at table below

4) Genital Ulcer Syndrome (GUS)

- Genital ulcer is an open sore or a break in the continuity of the skin or mucous membrane of the genitalia as a result of sexually acquired infections.
- Genital ulcer facilitates transmission of HIV more than other STI because it disrupts continuity of skins and mucous membranes significantly.
- The relative prevalence of causative organisms for GUD varies from place to place; hence clinical differential diagnosis of genital ulcers is inaccurate in places where there are several etiologies.

Etiology of Genital Ulcer Syndrome

- **HSV (HSV-1 and HSV-2)**
- Treponema pallidum
- Haemophilius ducreyi (Chancroid)
- Chlamydia trachomatis serovar L1, L2 & L3 (LGV)
- Klebsiella granulomatis

- Most cases of genital herpes are caused by HSV-2 in both males and females constituting 44% and 76% of the cases respectively.Moreover, dual infection with other genital ulcer pathogens is 52% of males and 78% of females.

Clinical presentations

- Clinical manifestation and patterns of GUS may vary with presence of HIV infection.
- Genital ulcer has different kinds of clinical manifestations due to different causatives.
- Common clinical manifestations of genital ulcer are:
  - ✓ Constitutional symptoms such as fever, headache, malaise and muscular pain
  - ✓ Recurrent painful vesicles and irritations
  - ✓ Shallow and non-indurated tender ulcers
  - ✓ Common sites in male are glance penis, prepuce and penile shaft
  - ✓ Common sites in women are vulva, perineum, vagina and cervix and can cause occasionally severe vulvo-vaginitis and necrotizing cervicitis
  - ✓ Painless indurated ulcer (Chancre)
  - ✓ Regional lymph adenopathy

Common causes of GUS

- **Genital herpes:**
  - ✓ HSV is the most common causes of genital ulcer worldwide.
  - ✓ It produces lifelong infection after the primary infection (latency).
  - ✓ The lesions are painful, erythematous macules which progressively form vesicles, pustules, ulcer and crusts.
- **Chancroid (ክርክር)**
  - ✓ Chancroid is also the common cause of genital ulcer in developing countries.
  - ✓ The lesion started as painful papules and pustules which ulcerate with dirty base and soft edge.
  - ✓ Inguinal fluctuant adenopathy (buboes) may occur following ulcer.
- **Syphilis:**
  - ✓ Clinically has three stages (primary, secondary, tertiary).
  - ✓ The ulcer starts during the primary stage of the disease as papules & rapidly ulcerate.
  - ✓ The ulcer is typically painless, clean base and raised boarder.
- **Lymphogranuloma veneurum (LGV):**
  - ✓ The disease starts as painless papules that develops an ulcer.
  - ✓ After a few days painful regional LAP develop and associated systemic symptoms may occur.
- **Granuloma inguinale (Donovanosis):**
  - ✓ It is chronically progressive ulcerative disease without systemic symptoms.
  - ✓ Presents with non-suppurative painless genital ulcer and beefy-red appearance

Complications of genital ulcer syndrome

- Locally destructive granulomatous lesions **(Gummas)** occur on the skin, liver, bones, or other organs
- **Tabes dorsalis** and **dementia**, often with paranoid features
- Latent meningovascular parenchymatous
- Optic atrophy
- General paresis
- **Aortic aneurysm and aortic valve insufficiency**
- **Asymptomatic aortitis**
- Angina pectoris
- **Recurrent disease**
- **Aseptic meningitis**
- **Encephalitis**
- **Phimosis in men**
- **Destruction of the penis or auto amputation**
- **Extra genital lesions**

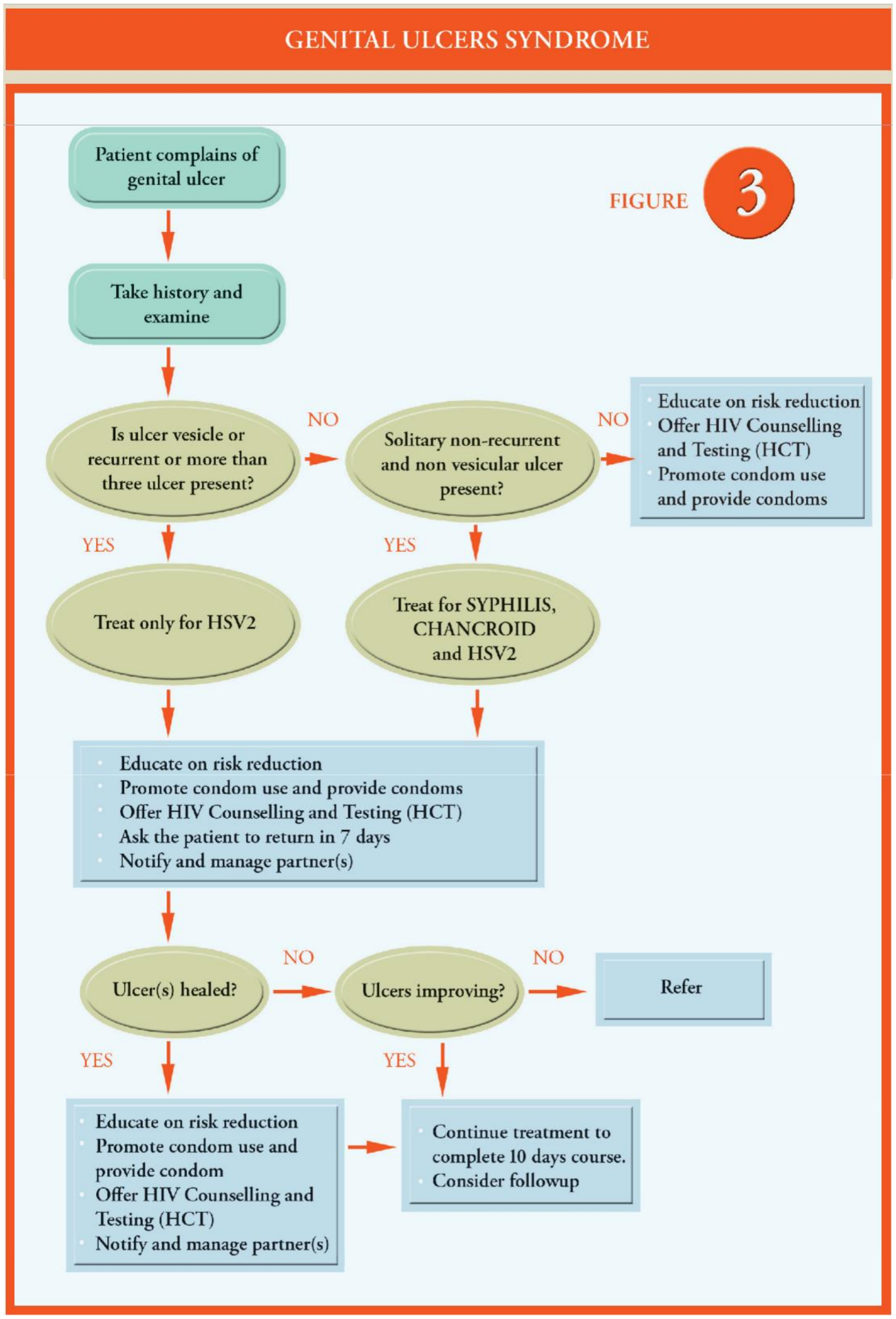

GENITAL ULCERS SYNDROME
FIGURE 3
Patient complains of genital ulcer
Take history and examine
Is ulcer vesicle or recurrent or more than three ulcer present?
NO
Solitary non-recurrent and non vesicular ulcer present?
NO
Educate on risk reduction
Offer HIV Counselling and Testing (HCT)
Promote condom use and provide condoms
YES
Treat only for HSV2
YES
Treat for SYPHILIS, CHANCROID and HSV2
Educate on risk reduction
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
Ask the patient to return in 7 days
Notify and manage partner(s)
Ulcer(s) healed?
NO
Ulcers improving?
NO
Refer
YES
Educate on risk reduction
Promote condom use and provide condom
Offer HIV Counselling and Testing (HCT)
Notify and manage partner(s)
YES
Continue treatment to complete 10 days course.
Consider followup

Figure: The algorithm of syndromic case management of genital ulcer syndrome

Treatment of genital ulcer syndrome

- To avoid the complications, some of which are life threatening as mentioned above, the syndrome must be treated aggressively and promptly.

Non-pharmacologic

- Prevent secondary infection by local cleaning

Pharmacologic

- Look at table below

5) Scrotal Swelling

- Inflammation of the epididymis usually manifests with acute onset of unilateral testicular swelling, often with tenderness of the epididymis and vas deferens, and occasionally with erythema and edema of the overlying skin.
- When it occurs in young male (<35 years old) accompanied with urethral discharge it is usually due to gonococcal or chlamydial infections.
- In older people the etiologic agent may be non-STIs such as E. coli, Klebsiella spp. or Pseudomonas.
- TB orchitis is generally accompanied by an epididymitis

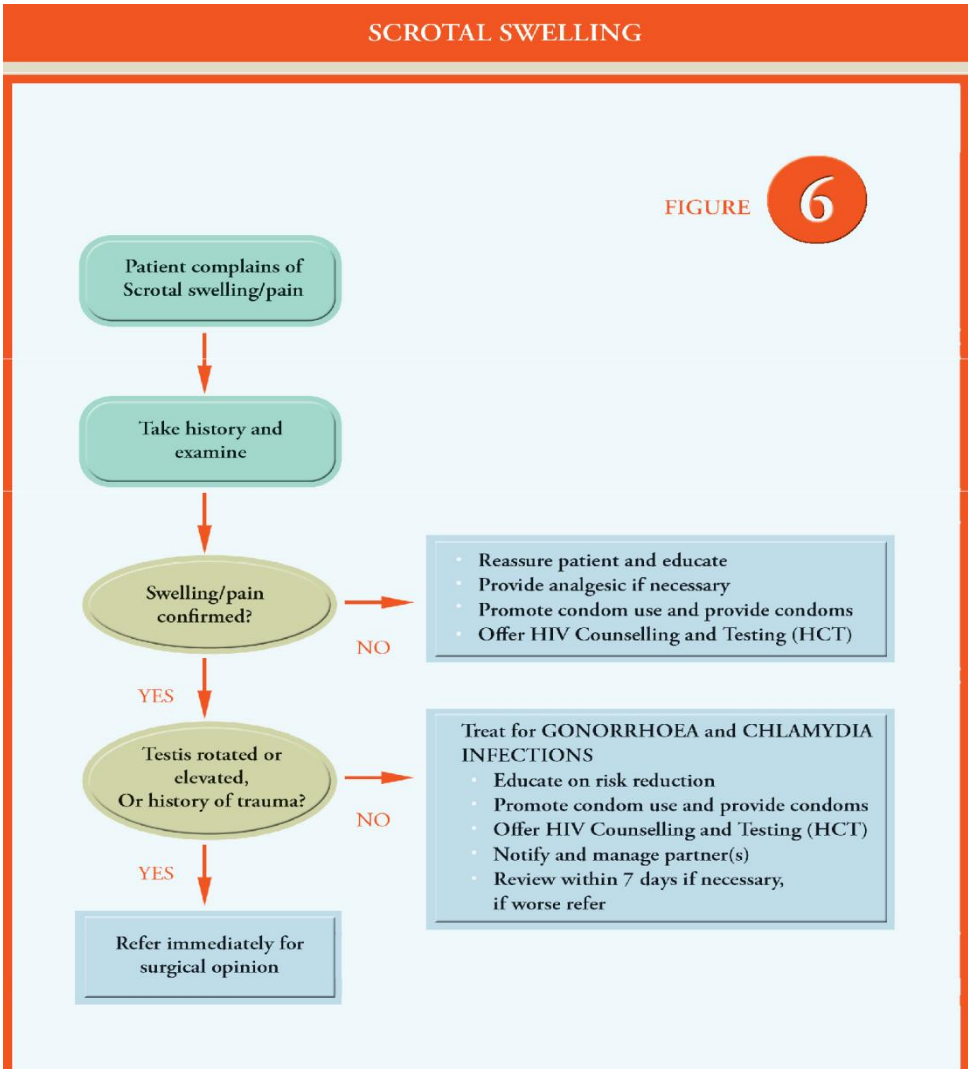

SCROTAL SWELLING
FIGURE 6
Patient complains of Scrotal swelling/pain
Take history and examine
Swelling/pain confirmed?
NO
Reassure patient and educate
Provide analgesic if necessary
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
YES
Testis rotated or elevated, Or history of trauma?
NO
Treat for GONORRHOEA and CHLAMYDIA INFECTIONS
Educate on risk reduction
Promote condom use and provide condoms
Offer HIV Counselling and Testing (HCT)
Notify and manage partner(s)
Review within 7 days if necessary, if worse refer
YES
Refer immediately for surgical opinion

Figure: The algorithm of syndromic case management of Scrotal Swelling

Treatment

- If quick and effective therapy is not given, the complications (Destruction and scarring of testicular tissues, infertility, impotence, and prostatitis) may occur.
- The treatment of scrotal swelling suspected of STI origin is similar to that of urethral discharge
- In addition, analgesia and scrotal support may be indicated as required.

Non-pharmacologic:

- Scrotal support

Pharmacologic

- Look at table below

6) Inguinal Bubo

- It is a painful, fluctuant, swelling of the lymph nodes in the inguinal region (groin).
- Buboes are usually caused by either chancroid or LGV.
- In many cases of chancroid, but not all, an associated ulcer is visible.
- Infection of the lower limb and other non-STIs like TB can also cause swelling of the inguinal lymph nodes.

Etiology → common causes of inguinal and femoral bubo are

- Chlamydia trachomatis (L1, L2 and L3) (causes LGV)
- Klebsiella granulomatis (donovanosis)
- Treponema pallidum (causes syphilis)
- Haemophilius ducreyia (causes chancroid)

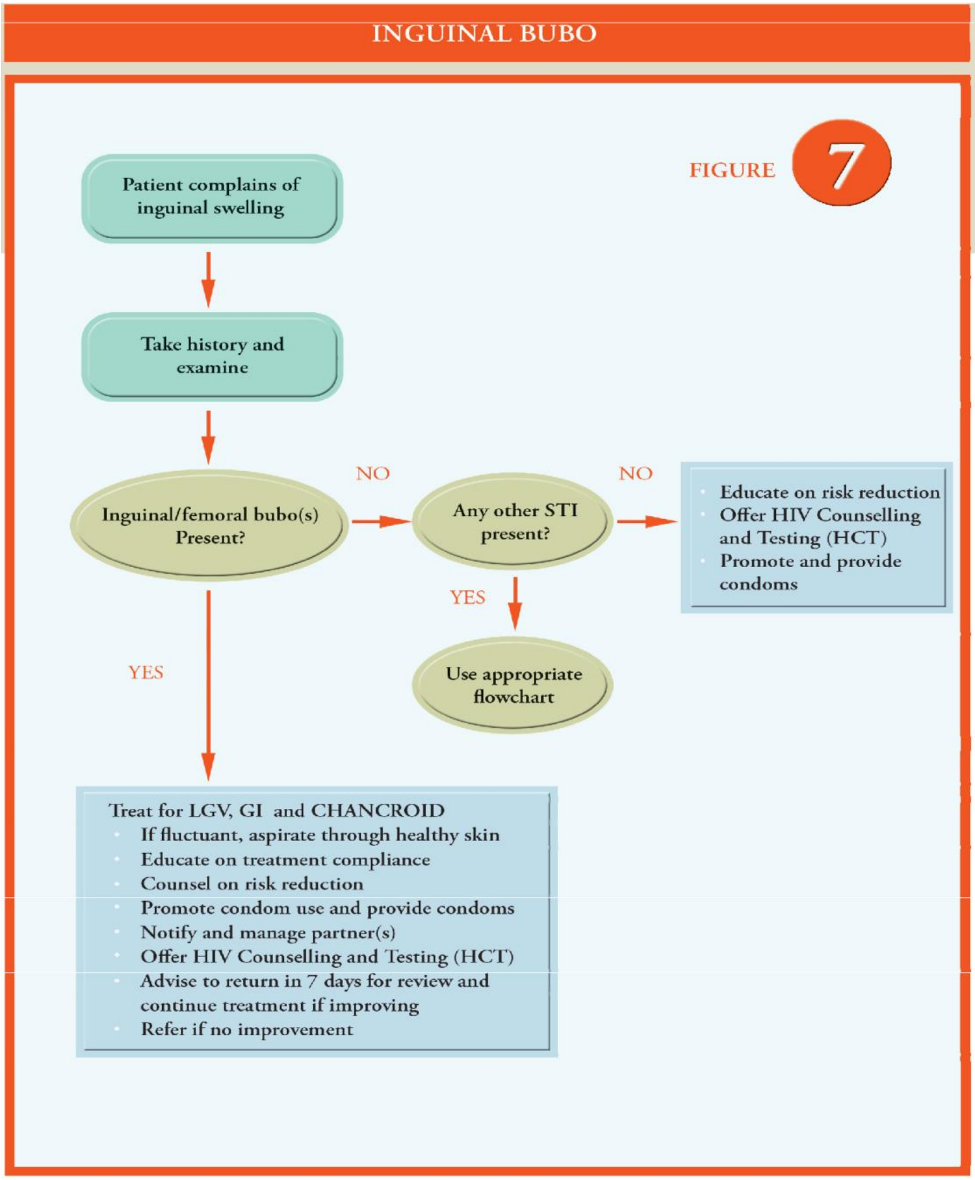

INGUINAL BUBO
FIGURE 7
Patient complains of inguinal swelling
Take history and examine
Inguinal/femoral bubo(s) Present?
NO
Any other STI present?
NO
Educate on risk reduction
Offer HIV Counselling and Testing (HCT)
Promote and provide condoms
YES
Use appropriate flowchart
YES
Treat for LGV, GI and CHANCROID
If fluctuant, aspirate through healthy skin
Educate on treatment compliance
Counsel on risk reduction
Promote condom use and provide condoms
Notify and manage partner(s)
Offer HIV Counselling and Testing (HCT)
Advise to return in 7 days for review and continue treatment if improving
Refer if no improvement

Figure: The algorithm of syndromic case management of urethral discharge syndrome

Treatment

Non pharmacologic:

- Keep the lesion clean and dry

Pharmacologic

- Look at table below

7) Neonatal conjunctivitis.

Refer updated NICU guideline

Syphilis (ቂጥኝ)

- Syphilis is caused by the bacterium Treponema pallidum.
- During initial stage of infection, the organism spreads widely, setting the point for consecutive manifestations.
- Syphilis is important health concern for women, especially HIV-infected women.
- Adverse pregnancy outcomes such as miscarriage or stillbirth, congenital syphilis in the new born and progression of latent syphilis in the mother are anticipated complications if the mother is left untreated.
- Thus, RPR test should be routinely done on pregnant mothers in their first trimester and treatment should be instituted if the rapid plasma regain (RPR) test is reactive.

Staging and clinical manifestations

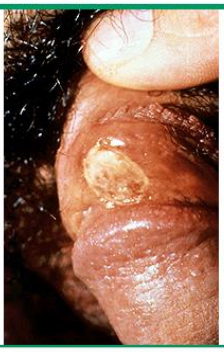
- Each stage of syphilis has characteristic clinical presentations not altered by pregnancy

i. Early syphilis

A. Primary syphilis: chancre (ክርኽር)

- ✓ Typically involves of a solitary **painless chancre** at site of inoculation, complemented by local adenopathy.

Primary syphilis: Penile chancre

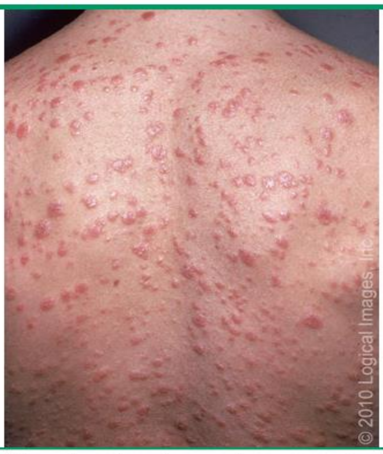


A chancre due to syphilis is an ulcerative lesion that is often painless and has an indurated character. Chancres arise at the site of initial inoculation of the organism.

B. Secondary syphilis:

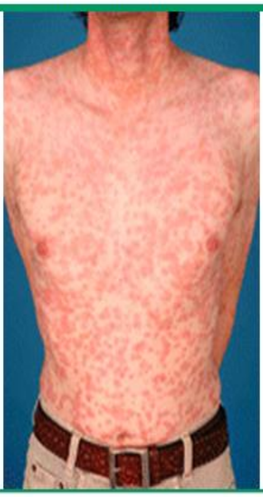
- ✓ A systemic illness often including a **rash** (The rash is classically a diffuse, symmetric macular or papular eruption involving the entire trunk and extremities including the palms and soles), **malaise, fever, and other** symptoms such as pharyngitis, mucous patches, hepatitis, condyloma lata, alopecia.

Secondary syphilis

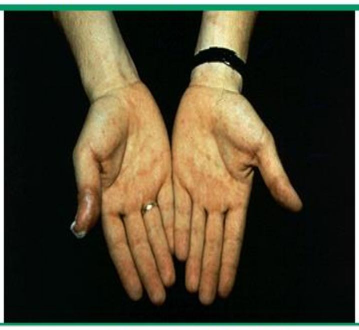


Multiple slightly scaly erythematous papules are present on the trunk of this patient with papular secondary syphilis.

Trunk rash secondary syphilis

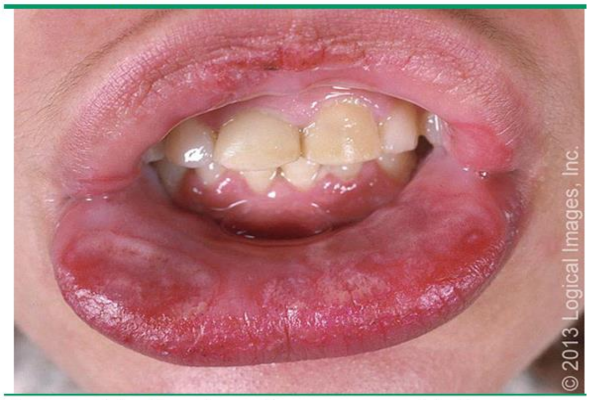


Secondary syphilis: Rash



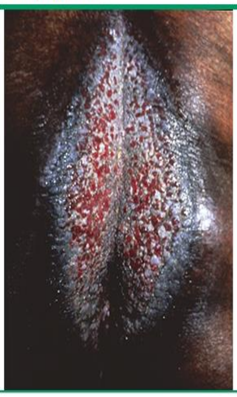
The rash of secondary syphilis characteristically involves the palms and soles. It may have a variety of appearances but is usually pigmented and macular.

Secondary syphilis: Mucous patch



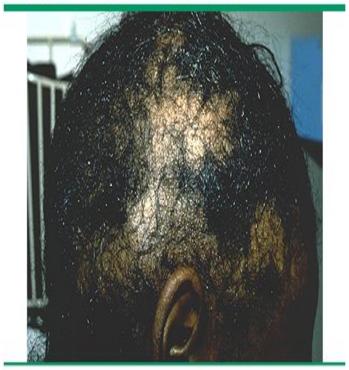
The mucous patches of secondary syphilis may appear on a variety of mucous membranes. They are teeming with organisms and are therefore highly infectious.

Condyloma lata in the perineal region of a woman with secondary syphilis



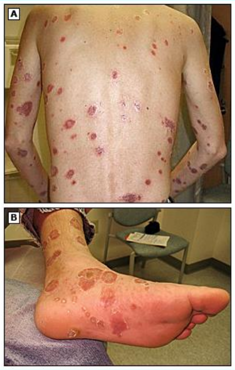
Numerous organisms are generally present in these lesions, which makes them highly infectious.

Patchy alopecia in secondary syphilis



Hair loss associated with secondary syphilis is usually patchy, producing a so-called moth-eaten appearance.

Secondary syphilis: Lues maligna



Lues maligna is a severe form of secondary syphilis that occurs in severely immunocompromised patients and is characterized by non-resolving ulcerative skin lesions.

C. Early latent:

- ✓ Period infection with *T. pallidum* as demonstrated by serologic testing, but **no symptoms**. Occurs **within first year** of initial infection.

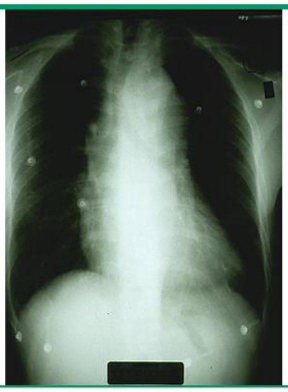
ii. Late syphilis

- Approximately 25 to 40% of patients with untreated syphilis can develop late disease.
- The clinical events may appear at any time from 1 to 30 years after primary infection.
- It is not necessary for individuals to have experienced clinically symptomatic primary or secondary syphilis prior to developing late syphilis
- **The most common manifestations** of late syphilis include:
  - ✓ Cardiovascular syphilis (especially **aortitis**)
  - ✓ **Gummatous syphilis** (granulomatous, nodular lesions which are rare, can occur in a variety of organs, usually skin and bones)
  - ✓ CNS involvement (particularly **general paresis and tabes dorsalis**)

D. Tertiary syphilis:

- Late syphilis with symptomatic manifestations involving the **CVS or gummatous disease** (granulomatous disease of skin and subcutaneous tissues, viscera, or bones).

Chest x-ray of tertiary cardiovascular syphilis



The characteristic lesion is a fusiform aneurysm of the thoracic aorta which almost always involving the ascending arch.

E. Late latent syphilis:

- Period of infection with *T. pallidum* as demonstrated by serologic testing, but **no symptoms.** Occurs **after one year** after initial infection, but if timing of infection is not known, late latent syphilis is presumed.

Neurosyphilis

- May happen at any time in the course of infection.

a. Early neurosyphilis:

- may have asymptomatic meningitis; symptomatic meningitis; or less commonly meningovascular disease (ie, meningitis and stroke).
- Vision or hearing loss with or without concomitant meningitis may also be present, and ocular/otologic syphilis is treated as neurosyphilis.

Uveitis and vitritis secondary to syphilis

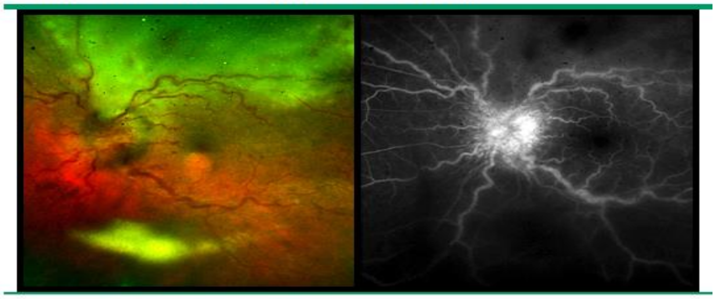


Photo of retina (color and after intravenous fluorescien dye) in a patient with uveitis and vitritis secondary to syphilis. The optic nerve is swollen (blurring of the optic disc margens), there is retinal edema and necrosis (retina appears white and elevated) as well as retinal vasculitis and tortuous vessels coming from the optic nerve. In addition, the presence of significant vitritis gives the picture a general haze (due to inflammatory cells floating in the vitreous).

b. **Late neurosyphilis:**

- The most common forms involve brain and spinal cord (dementia - general paresis and tabes dorsalis).

Complications of syphilis

- If untreated, Syphilis have a number of significant late manifestations or complications, including cardiovascular, gummatous, and neurologic cxn.

Investigations (screening and diagnosis)

- **Diagnostic testing** should be made for all patients with signs and symptoms of syphilis.
- Asymptomatic patients had better be **screened** for syphilis if at high risk for acquired disease or for transmitting infection to others (eg, pregnancy).

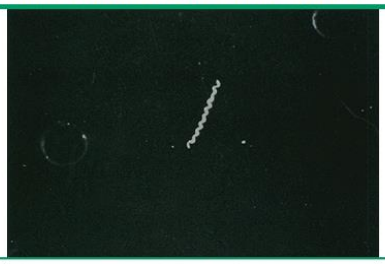
DIAGNOSTIC TESTS

- **Serologic tests**
  - ✓ Serologic tests provide a presumptive diagnosis of syphilis.
  - ✓ There are **two types** of serologic tests for syphilis: **nontreponemal tests and treponemal-specific tests.**
- **Nontreponemal tests include:**
  - ✓ Rapid plasma reagin (RPR)
  - ✓ Venereal Disease Research Laboratory (VDRL)
  - ✓ Toluidine Red Unheated Serum Test (TRUST)
- **Specific treponemal tests include:**

  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Micro hemagglutination test for antibodies to *T. pallidum* (MHA-TP)
  - *T. pallidum* particle agglutination assay (TPPA)
  - *T. pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)
- Direct methods for diagnosis
  - Direct methods can be used to provide a definitive diagnosis of syphilis.
  - Since *T. pallidum* cannot be cultured in the laboratory, the organism must be identified through direct visualization or detection in clinical specimens.

i. **Darkfield microscopy** and **direct fluorescent antibody (DFA)** testing can be used to detect the organism;
  - However, neither of these tests are routinely available in clinical settings because these methods require special equipment to perform the test, as well as considerable experience and expertise to properly interpret the results.

Treponoma pallidum by darkfield microscopy



Darkfield examination of an exudate from a penile ulcer in a patient with syphilis. When viewed in a fresh specimen, Treponema pallidum moves with a characteristic forward and backward motion with rotation around the longitudinal axis.

ii. PCR

Diagnosis and interpretation of results

- Diagnostic evaluation for syphilis is the same in pregnant and nonpregnant women.
- A diagnosis of syphilis is made using serologic testing of blood specimens (presumptive diagnosis than definitive).
- A diagnosis is made when both **nontreponemal and treponemal tests** are reactive.
- Nevertheless, either test can be used as the initial screening test. But due to high possibility of false positive screening test results, confirmatory testing is necessary.
- If **neurosyphilis** considered, additional **CSF analysis** should be performed.

- **Appropriate interpretation of serologic testing** (depends on clinical disease presence or absence, patient's prior syphilis history, and individual's immune status):
  - ✓ **If no prior syphilis history:** diagnosis made **if both** nontreponemal & treponemal tests are reactive.
  - ✓ **If has history of treated syphilis:** a positive **nontreponemal test** may suggest a new infection, evolving response to recent therapy, treatment failure, or presence of a serofast state.
- **False positive and false negative results**
  - ✓ A positive nontreponemal test followed by a negative treponemal test: generally considered a false positive result.
  - ✓ An initial treponemal-specific screening may have a positive treponemal test followed by a negative nontreponemal test. This is usually seen for previously treated syphilis. Also, in very early syphilis (occasional), or in late syphilis when nontreponemal tests become nonreactive over time.
  - ✓ Patient with clinical signs and symptoms of early syphilis (eg, ulcer, rash) may have false negative result for initial nontreponemal test, classically due to testing prior to antibody formation or secondary to a prozone effect.
- **Latent syphilis:** diagnosed if no clinical signs or symptoms of syphilis but has serologic evidence of infection. Early or late latent depending upon duration of infection- if duration unknown considers it as late syphilis.
- **All diagnosed cases of new syphilis should be treated, tested for HIV and other STD.**

Screening

- Pregnant women should be screened for syphilis.
  - ✓ False-positive screening tests may be more common in the setting of pregnancy. Thus, confirmatory testing must be performed (algorithm)
- asymptomatic patients should be screened for syphilis if they are at high risk for having acquired disease or for transmitting disease to others.

Pre-treatment evaluation

- A nontreponemal titer should be obtained just before starting therapy (preferably, on the first day of therapy) since titers can increase significantly over a few days between diagnosis of syphilis and treatment initiation.

Treatment

- **Penicillin remains the gold standard** treatment for syphilis in both pregnant and nonpregnant patients appropriate for their stage of infection.
- Parenteral (IM or IV) penicillin G is the **only** therapy with recognized efficacy and safety for both mother and fetus during pregnancy. It is effective for treating maternal disease, preventing transmission to the fetus, and treating established fetal disease.
- Alternatives are not as safe for pregnant woman or fetus or not as effective for prevention of congenital syphilis. Hence, if possible, desensitize allergic patients and treat with IV penicillin.

Table: Treatment of syphilis for pregnant and non-pregnant adults with normal renal function

Stage of syphilis*	Treatment N.B If possible, desensitize allergic patients and treat with IV penicillin	
	Non-pregnant adults	Pregnant adults
Early syphilis (Primary/secondary/early latent) < 2 years duration	**Firs line:** ➢ Benzathine Penicillin G 2.4 million units IM stat **Alternatives:** ➢ Ceftriaxone 1 - 2g IV/IM daily for 10 to 14 days or ➢ Erythromycin 500 mg PO QID for 14 days or ➢ Doxycycline 100 mg PO BID for 14 days or ➢ Tetracycline 500 mg po QID for 14 days or ➢ Amoxicillin 3 g plus probenecid 500 mg, both given PO BID for 14 days	➢ Benzathine Penicillin G (Bicillin L-A) 2.4 million units(MU) IM Stat (administer as 1.2 MU in each buttock) **If serologic failure on follow-up:** ➢ additional follow-up not assured, Prompt CSF and retreating as late syphilis is recommended.
Late syphilis (Late latent/tertiary/unknown duration) > 2 years duration	**Firs line:** ➢ Benzathine Penicillin G 2.4 million units IM once weekly for 3wks **Alternatives** ➢ Ceftriaxone 2g IV/IM daily for 10 to 14 days or ➢ Erythromycin 500 mg PO QID for 30 days or ➢ Doxycycline 100 mg PO BID for 4 weeks	➢ Benzathine Penicillin G (Bicillin L-A) 2.4 million units IM once weekly (administer as 1.2 MU in each buttock) for 3 weeks (7.2 million units total dose) **If a dose is missed for > 14 days,** ➢ restart the full 3 dose course of therapy.

Neurosyphilis (including ocular syphilis)	**First line:** ➢ Aqueous penicillin G 3 to 4 million units IV every four hours (or 18 to 24 million units continuous IV infusion) for 10 to 14 days or ➢ Penicillin G procaine 2.4 million units IM daily plus probenecid 500 mg PO QID, both for 10 to 14 days ➢ **If possible, desensitize allergic patients and treated with IV penicillin** **Alternatives:** ➢ Ceftriaxone 2 g IV daily for 10 to 14 days OR ➢ doxycycline 200 mg PO BID for 21 to 28 days (If no ceftriaxone or allergic to it)	➢ Aqueous crystalline penicillin G 3 to 4 Million Units IV every 4 hours or as a continuous infusion over 24 hours (18 to 24 MU/day) for 10 to 14 days OR ➢ Penicillin G procaine 2.4 million units IM once daily (usually administered as 1.2 MU in each buttock) plus probenecid 500 mg PO QID, both for 10 to 14 days
	➢ *After IV treatment completion, single dose of 2.4 million Units* Benzathine Penicillin G *(for non-pregnant) and once/week for 3 weeks (pregnant) can be used*	
Post-exposure prophylaxis	See discussion below	➢ Penicillin G benzathine (Bicillin L-A) 2.4 million units IM stat (administer as 1.2 MU in each buttock)
*The National STI Guideline (2015) consider and manage a history of non-reactive RPR test within the past 2 years as early syphilis and infections more than two years ago or no prior history of non-reactive RPR test (unknown duration) as late syphilis.		

Complications of treatment among pregnants

- **Jarisch-Herxheimer reaction:**
  - ✓ this may precipitate uterine contractions, preterm labor, and/or no reassuring fetal heart rate (NRFHR) tracing in pregnant women treated in the 2nd TM of pregnancy.
  - ✓ Provide supportive care of maternal distress and standard obstetric management of pregnancy complications.

Follow-up

- Monitor **clinically and with serologic testing** after treatment to ensure response.
- **Frequency of follow up and interpretation of nontreponemal titers;**

- **Frequency of serologic monitoring depends on stage of disease & existence of HIV:**
  - ✓ In **HIV-uninfected with early syphilis:** test at **6 and 12-months** following treatment and at any time if clinical symptoms recur. In general, such patients experience adequate response by 12 months.
  - ✓ **HIV-uninfected with late syphilis:** follow-up serologic testing at **6, 12, and 24 months.** Some with late syphilis may not have adequate response for up to 2 years after treatment.
  - ✓ **HIV co-infected**: should be monitored **more frequently**.
  - ✓ **Neurosyphilis**: Monitored **at same frequency as without neurosyphilis.** Additional, **monitoring of CSF** abnormalities is necessary.
  - ✓ **Pregnant women**; follow-up frequency is **the same to non pregnants** and depends on stage of disease and HIV coinfection.

- The same test, preferably RPR, should be done each time and at the same laboratory.
- A 4 times increase in nontreponemal titer after treatment is always abnormal.
- A 4 times decrease in titer, equivalent to a change of two dilutions (such as from 1:16 to 1:4 or 1:32 to 1:8), is considered as acceptable response to therapy; but this may take months to attain.
- For pregnant a fall in maternal titers does not guarantee that fetal treatment has been adequate.
- Over time, most successfully treated syphilis patients experience seroreversion; but some may remain serofast.

Handling treatment failure

- Suspect failure if nontreponemal titers do not decline ≥ 4 times, or if 4 times increase after an initial decline.
- If no adequate response to treatment, determine if reinfected, experiencing a slow response to treatment, or has failed treatment.
- Treatment failure is likely due to poor adherence, alternative agent use, immunosuppressed status, or unrecognized CNS disease.

Treatment after an exposure

Sexually partners:

- Should be evaluated clinically and serologically for evidence of infection.
- Empiric treatment requirement depends primarily upon when the exposure occurred and the stage of their partner's infection.

Vertical transmission (VT)

- Frequency is higher with early than late stage syphilis.
- Among women who acquire syphilis during pregnancy, the risk of VT increases with increasing gestational age at acquisition of maternal infection.
- Fetal infection should be suspected if there are characteristic findings on ultrasound examination after 20 weeks of gestation in a woman with untreated or inadequately treated syphilis.
- Hepatomegaly and placentomegaly are early findings suggestive of congenital syphilis. Anemia, ascites and hydrops occur later in course of fetal infection. An abnormal ultrasound is not diagnostic and the normal also does not exclude fetal infection.

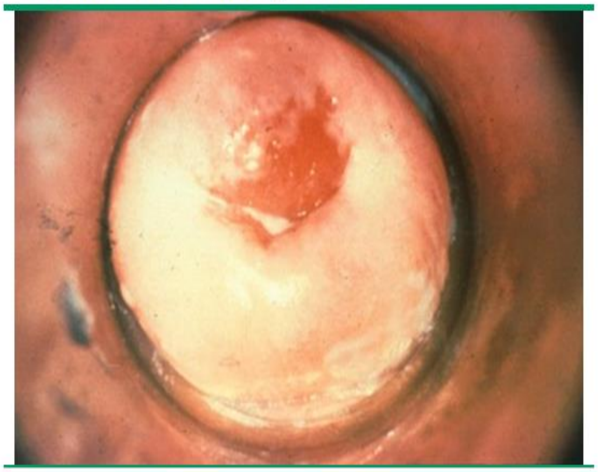
Fetal treatment

- Maternal penicillin treatment is curative for fetal infection in most cases.
- A maternal treatment ≤ 30 day before delivery is a risk factor for congenital infection.
- A maternal treatment with non-penicillin agents is also a risk factor.
- **Aqueous crystalline penicillin G 50, 000 units/kg IV TID for 10-15 days OR procaine penicillin G 50,000 units/kg IM daily for 10 -15 days for prevention (at risk cases) and treatment of congenital syphilis.**

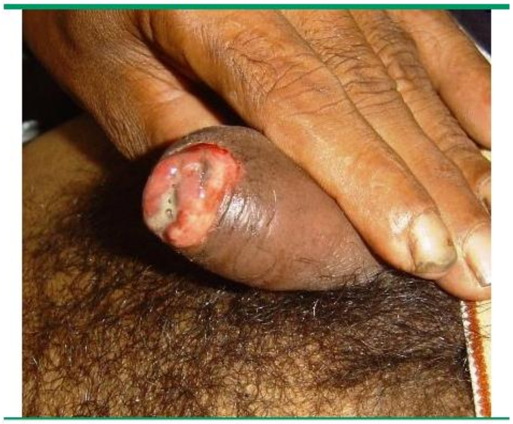
Gonorrhea (ጨብጥ)

- Gonorrhea is an infection with the gram-negative coccus *Neisseria gonorrhoeae*
- Gonorrhea is a major cause of urethritis in men and cervicitis in women; the latter can result in PID, infertility, ectopic pregnancy, and chronic pelvic pain.
- Gonococcal infections, including urethritis, cervicitis, epididymitis, and proctitis, are a significant cause of morbidity among sexually active men and women worldwide.
- Urogenital, anogenital, pharyngeal, and ocular gonococcal infections that are not associated with bacteremia or ascending spread of the pathogen to other organs are considered **uncomplicated.**
- Extragenital infections of the pharynx and rectum are prevalent in certain groups, such as men who have sex with men (MSM).
- Invasive infections with *N. gonorrhoeae*, including disseminated gonococcal infection, endocarditis, and meningitis, are uncommon but can result in serious morbidity **(complicated)**

Cervicitis in a woman with gonorrhea

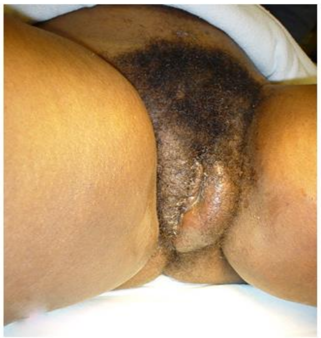


Gonococcal urethritis



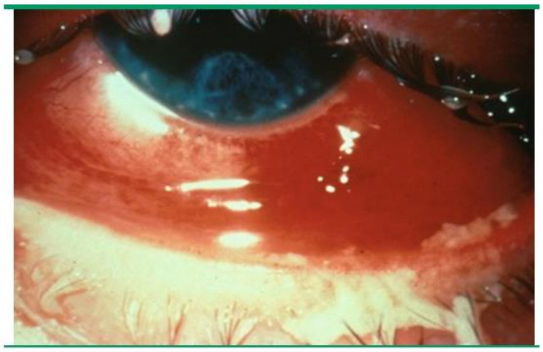
This 23-year-old man complained of profuse and purulent penile discharge with dysuria five days after unprotected sexual contact. Gram stain of the urethral discharge showed polymorphonuclear cells with intracellular Gram negative diplococci.

Bartholin abscess



The patient's left labial area is swollen and erythematous.

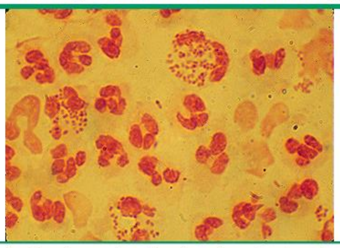
Gonococcal conjunctivitis in an adult



DIAGNOSTIC APPROACH

- **Clinical syndrome approach (preferred in our setup) →** which can manifest as VDS, UDS, PID, conjunctivitis…
- nucleic acid amplification testing **(NAAT)** is the test of choice for the initial microbiologic diagnosis of *N. gonorrhoeae* infection, although **culture** remains an important diagnostic tool when antibiotic resistance is suspected.
- If NAAT methods are unavailable, microscopy (for men), culture, antigen detection, and genetic probe methods can be used with **endocervical or urethral swabs.**

Gram stain of gonococcus in urethral discharge



Gram stain of purulent exudate from the male urethra (x1000) shows polymorphonuclear leukocytes containing numerous intracellular gram-negative diplococci. As expected, *Neisseria gonorrhoeae* grew from this specimen.

Management

A. Syndromic approach is recommended (refer mgt of VDS, UDS, PID)

B. Mgt based on specific diagnosis

i. Uncomplicated gonorrhea: Cervicitis, proctitis, urethritis, pharyngitis:

First line

- ✓ Ceftriaxone 250mg IM stat plus
- ✓ azithromycin 1g po stat

Alternatives

Patients with severe cephalosporin allergy

- ✓ azithromycin 2 g PO stat
  plus
- ✓ gentamicin 240mg IM stat or
- ✓ Gemifloxacin 320mg PO stat

If ceftriaxone unavailable

- ✓ Cefixime, 400 mg as a single dose in combination with oral azithromycin
  - **Not recommended due to limited efficacy**

ii. Conjunctivitis

- ✓ Ceftriaxone 1 g IM stat plus
- ✓ Azithromycin 1 g PO stat

additionally, consider a one-time saline lavage of the infected eye for conjunctivitis.

iii. Disseminated gonococcal infection (arthritis and arthritis-dermatitis syndrome)

- ✓ Ceftriaxone 1g IV/IM daily

  - Duration; for **24 to 48 hours** after clinical improvement, then may **switch to an oral agent** guided by antimicrobial susceptibility to complete a **total of at least 7 days** of therapy

plus

- ✓ Azithromycin 1 g PO stat

iv. **Gonococcal Endocarditis**

- ✓ Ceftriaxone 1 to 2 g daily or BID for at least 28 days plus
- ✓ Azithromycin 1 g PO stat

v. **Gonococcal Meningitis:**

- ✓ Ceftriaxone 1 to 2 g daily or BID for 10 to 14 days plus
- ✓ Azithromycin 1 g PO stat

Gonococcal infection, expedited partner therapy

- ✓ Ceftriaxone 250mg IM stat plus
- ✓ azithromycin 1g po stat

Note:

- To be used only for heterosexual partners with gonorrhea if health department partner-management strategies are impractical/unavailable and there is concern by the provider for the prompt evaluation and treatment of the partner
- Provide written materials to educate partners about their exposure to gonorrhea, importance of therapy, and when to seek clinical evaluation for adverse reactions/complications

Treatment failure

- **Note:** Reinfections are more likely to occur than actual treatment failures,
- Re-treatment with preferred dual-therapy regimen is recommended for re-infection.
- Choice of agent (e.g. ceftriaxone, Gemifloxacin, or gentamicin) to combine with azithromycin following treatment failure varies considerably

depending on the failed initial dual-therapy regimen, susceptibilities of isolate, and geographic location

Management of Treatment failure

- Treatment failure following single-therapy regimen or other non-preferred treatment regimens:
  - ✓ Ceftriaxone 250mg IM stat plus
  - ✓ azithromycin 1g po stat
- Treatment failure following initial therapy of an alternative dual therapy regimen (cefixime and azithromycin):
  - ✓ Ceftriaxone 250mg IM stat plus
  - ✓ azithromycin 2g po stat
- Treatment failure following initial therapy of the preferred dual-therapy regimen (ceftriaxone and azithromycin):
  - ✓ Ceftriaxone 500mg IM stat plus
  - ✓ azithromycin 2g po stat

Table; Pharmacologic Treatment of STI

Type of STI	**Treatment** N.B For all STI, in addition to treatment, educate the patient on ➢ Abstinence from sex and avoiding alcohol intake till all symptoms resolve and management completed ➢ Sex Partner notification and management based on type of STI and indication ➢ Importance of HIV testing ➢ Proper and consistent use of condom ➢ Risk reduction ➢ Treatment compliance	
	Risk assessment +ve	**Risk assessment -ve**

Vaginal Discharge Syndrome	➢ **Ceftriaxone 250mg IM stat** or ➢ Ciprofloxacin 500mg po stat or ➢ Spectinomycin 2 gm IM stat PLUS ➢ **Azithromycin 1gm po stat** or ➢ Doxycycline 100 mg po bid for 7 days PLUS ➢ **Metronidazole 500 mg bid for 7 days** **If discharge is white or curd-like add > Clotrimazole vaginal pessary 200 mg at bed time for 3 days** **Note: The preferred regimen is Ceftriaxone 250mg IM stat + Azithromycin 1gm po stat + Metronidazole 500 mg bid for 7days**	➢ Metronidazole 500 mg bid for 7 days If discharge is white or curd-like add ➢ Clotrimazole vaginal pessary 200 mg at bed time for 3 days OR ➢ Miconazole vaginal pessary 200mg at bed time for 3 days.
	Sex Partners ➢ Examination and treatment usually not necessary if the risk assessment is negative. ➢ However, treatment with an imidazole cream (e.g, miconazole, clotrimazole) may be indicated in some cases of recurrent infection, or if the partner has penile candidiasis (Balanitis).	
	Outpatients	**In patients**

Lower Abdominal Pain	➢ **Ceftriaxone** 250 mg IM stat or ➢ Ciprofloxacin, 500mg po stat or ➢ Spectinomycin 2gm IM stat PLUS ➢ **Azithromycin** 1gm po stat or ➢ Doxycycline 100 mg po BID for 14 days PLUS ➢ **Metronidazole** 500 mg po BID for 14 days Note: The preferred regimen is ➢ Ceftriaxone 250mg IM stat PLUS ➢ Azithromycin 1gm po stat PLUS ➢ Metronidazole 500 mg bid for 14 days Admit if there is no improvement within 72 hours	➢ Ceftriaxone 250 mg IM/IV or ➢ Spectinomycin 2 gm IM BID PLUS ➢ Azithromycin 1gm po daily or ➢ Doxycycline 100 mg po BID for 14 days PLUS ➢ Metronidazole 500 mg po BID for 14 days Note: For inpatient PID, ceftriaxone, spectinomycin or azithromycin should continue for 24hrs after the patient remain clinically improved, after which doxycycline and metronidazole should continue for a total of 14 days
Urethral Discharge Syndrome	**First line (preferred)** ➢ Ceftriaxone 250mg IM stat plus ➢ Azithromycin 1gm po stat **Alternative** ➢ Ciprofloxacin, 500mg PO stat or ➢ Spectinomycin 2 gm IM stat PLUS ➢ Doxycycline 100 mg po bid for 7 days or ➢ Tetracycline 500 mg po QID for 7 days or ➢ Erythromycin 500 mg po QID for 7 days (in cases of contraindications for Tetracycline. e.g. for children and pregnancy) **NB:** ➢ Patients should be advised to return if symptoms persist for 7 days after the initiation of treatment. ➢ Single dose treatment is encouraged as much as possible	
Persistent/Recurrent Urethral Discharge	➢ Re-treat with initial regimen ✓ If non-compliant or re-exposure occurs, re-treat with the initial regimen with due emphasis on drug compliance and/or partner management. ✓ Cover M. genitalium and T. vaginalis ➢ If compliant with initial regimen and re-exposure can be excluded, the recommended drug for persistent or recurrent urethral discharge syndrome in Ethiopia is: ✓ **Metronidazole 2 gm po. Stat** or ✓ **Tinidazole 1gm po once for 3 days (Avoid Alcohol!)**	

	PLUS ✓ **Azithromycin 1g PO, stat** (only if not used during the initial episode to address doxycycline resistant M.genitalium) ➢ Despite all these treatments, if symptoms still persist to require treatment with a new antibiotic regimen and a sexually transmitted agent is the suspected cause, all partners in the past 3 months before the initial diagnosis and any interim partners should be consulted to a gynecologist for evaluation and appropriate treatment of treatment failure.
Genital Ulcer Syndrome (GUS)	A. Treatment for **non- vesicular genital ulcer** ➢ Benzathine penicillin, 2.4 million units IM stat or ➢ Doxycycline (in penicillin allergy) 100mg bid for 14 days PLUS ➢ Ciprofloxacin 500mg PO bid for 3 days or ➢ Erythromycin 500mg PO QID for 7 days PLUS ➢ Acyclovir 400mg PO, TID for 10 days (or 200 mg 5 times per day of 10 day) B. Treatment for **vesicular, multiple or recurrent genital ulcer** ➢ Acyclovir 400 mg PO TID for 7 days or 200 mg 5 times per day for 10 days N.B. There is no medically proven role for topical acyclovir, its use is discouraged. C. Treatment for **recurrent infection episodes**: ➢ Acyclovir 400 mg P.O. TID for 5 to 7 days, Treatment should be initiated during prodrome or immediately after onset of symptoms. Local care: Keep affected area clean and dry D. **Suppressive** treatment: recommended for patients **with ≥ 6 recurrences per year** ➢ Acyclovir, 400mg P.O. BID for 1 year N.B. The need for continued suppressive therapy should be reassessed.
Scrotal Swelling	**First line (preferred)** ➢ Ceftriaxone 250mg IM stat plus ➢ Azithromycin 1gm po stat **Alternative** ➢ Ciprofloxacin, 500mg PO stat or ➢ Spectinomycin 2 gm IM stat PLUS ➢ Doxycycline 100mg po bid for 7 days or ➢ Tetracycline 500 mg po QID for 7 days or

	➢ Erythromycin 500 mg po QID for 7 days (in cases of contraindications for Tetracycline e.g. for children and pregnancy)
Inguinal Bubo	**First line** ➢ Ciprofloxacin, 500mg P.O, BID for 3days PLUS ➢ Doxycycline, 100mg P.O, BID for 14days OR ➢ Erythromycin, 500mg, P.O, QID for 14days If patient have genital ulcer, add ➢ Acyclovir 400mg PO TID for 10 days (or 200mg 5 times per day for 10 days) ➢ N.B. Fluctuant lymph nodes should be aspirated through healthy skin but incision and drainage or excision of nodes may delay healing and should not be attempted ➢ If there is doubt with diagnosis and/or treatment failure ✓ Do culture and sensitivity test, if available DNA PCR and treat accordingly.

Prevention of STIs

- Comprehensive approach to STI prevention includes
  - ✓ Risk assessment with counseling
  - ✓ Vaccination
  - ✓ Identification of infected individuals and effective treatment with follow-up
  - ✓ Evaluation and treatment of sexual partners.

- **Accurate risk assessment, education and counseling of at-risk individuals to avoid STIs**
  - ✓ Carefully obtain routine sexual histories for proper screening and prevention counseling.
  - ✓ Behavioral risk factors include:
    - New or multiple sex partners
    - sex partners with recent STI no or inconsistent condom use outside a monogamous sexual partnership, Commercial sex work for money or drugs
    - Sex workers or sexual contact with them
  - ✓ Careful evaluation of adolescents and pregnant is important for the high risk for STI.
  - ✓ All individuals evaluated for STI screening or diagnosis should be tested for HIV infection.
  - ✓ Patient-centered risk reduction counseling:
    - assess patient's understanding of STI transmission risk

        - discuss risk of patient's sexual behavior
        - assessing patient's willingness to change behaviour, have shared goal for behavioral change, with clear & realistic steps.
    - ✓ **Prevention may include abstinence, mutual monogamy, barrier methods (Male and female condoms).**
    - ✓ Use of male condoms has been associated with a reduced risk for HIV, chlamydia, gonorrhea, HSV, and HPV transmission.

Vaccination

- ➢ Pre-exposure vaccinations of at-risk individuals for vaccine-preventable infections avoid several sexually transmitted or associated infections:
    - ✓ **Hepatitis A virus (HAV)** vaccine→ individuals with CLD, and those with risk factors for HAV infection (like illicit drug use).
    - ✓ **Hepatitis B virus (HBV)** vaccine → for nonimmune individuals with STI risk factors, comprising injection drug users and HIV-infected ones.
    - ✓ **Human papillomavirus (HPV)** vaccine→ Gardasil have recently been developed to prevent HPV type 16 and 18 infections which are associated with 80% of cervical cancer. It is offered to all girls who are age 14 in Ethiopia.
    - ✓ **Meningococcal vaccine**→ for persons exposed to outbreaks, HIV-infected ones, among others.
- ➢ **Identification of both asymptomatic and symptomatic individuals with STIs can avoid unrecognized transmission.**
- ➢ **Effective diagnosis, treatment, counseling, and follow-up of infected individuals is also critical component of STI prevention.**
- ➢ **Sex partners of infected individuals should also be evaluated, treated, and counseled to prevent persistent infection transmission.**

Other prevention methods:

- ➢ **Male circumcision**: may reduce HIV acquisition; also decrease risk of HSV and HPV infection.
- ➢ **Antimicrobial-based prevention** may include:
    - ✓ antiretroviral treatment (preexposure prophylaxis, and post-exposure prophylaxis, to prevent HIV infection)
    - ✓ Suppressive antiviral therapy for genital herpes simplex virus (HSV) can prevent transmission.

3.12.5 Sepsis

- Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.

- Sepsis and septic shock are the major causes of morbidity and mortality worldwide.
- The morbidity and mortality seems higher among extreme age groups (neonates and elderly) than adults.

Cause

- ✓ Sepsis is caused by an immune response triggered by an infection.
- ✓ The infection is most commonly bacterial. Fungi, viruses, or parasites can also cause sepsis.
- ✓ The most common primary sources that leads to sepsis was respiratory tract, brain, urinary tract, skin, and abdominal organ infections.
- ✓ RF for sepsis
  - Young or old age
  - a weakened immune system from conditions such as cancer or diabetes
  - major trauma or burns

Clinical presentations

Common signs and symptoms of include

- ✓ Fever,
- ✓ Tachycardia
- ✓ Tachypnoea
- ✓ confusion.
- ✓ There may also be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection.
- ✓ In the very young, old, and immunocompromised patients, symptoms of a specific infection may not present and the body temperature may be low or normal rather than high.

Investigation and diagnosis

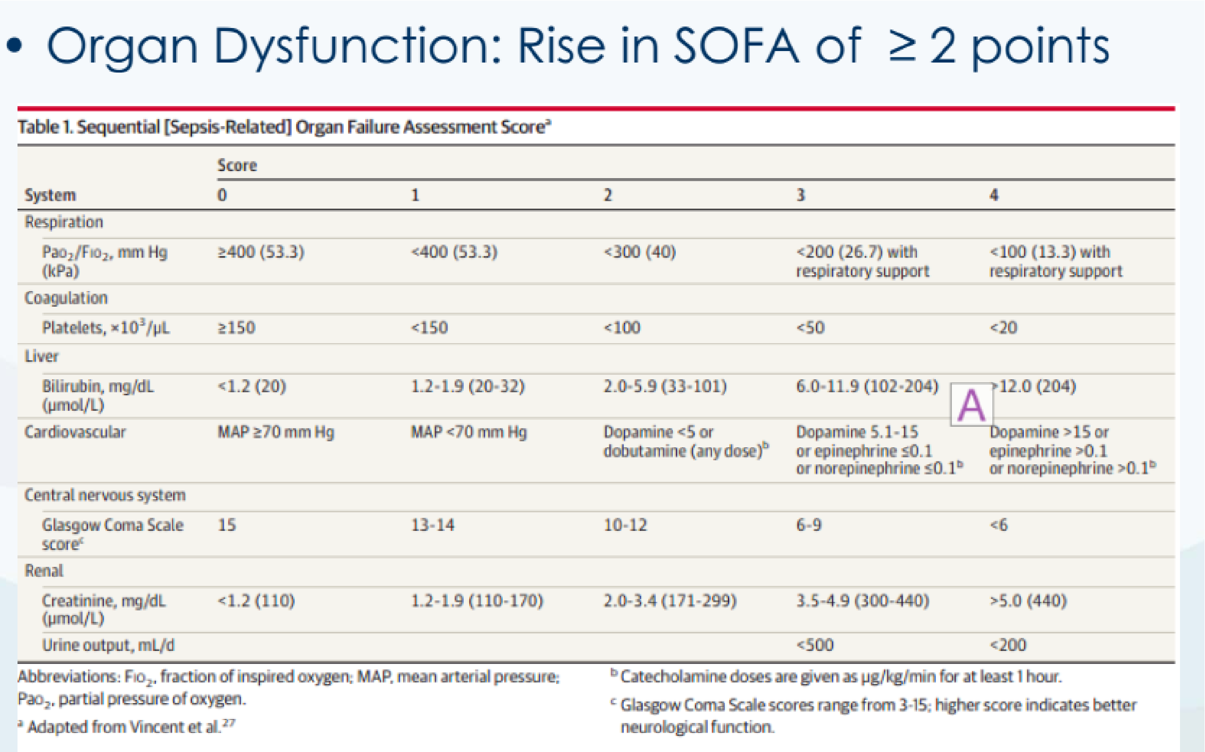
- The diagnosis of sepsis depends on
  - Age
  - clinical presentation
  - types of infection and other factors.
- Different screening tools were available for Sepsis. This may include
  1. **SIRS** (Systemic Inflammatory Response Syndrome) → no more used
  2. **SOFA** (sequential Organ Failure Assessment)
  3. quick SOFA **(qSOFA).**

❖ However, they may need validation to the local contexts as they were developed based on western patient data.

Quick SOFA (qSOFA) score.

- Given the limitations an adult patient with suspected infection can be quickly screened for likelihood of having poor outcomes if they have **at least 2** of the following 3 clinical criteria (**qSOFA**):
    1. RR ≥ 22 BPM
    2. SBP ≤ 100 mmHg
    3. Altered mentation.
- This simple bedside risk stratification tool (**qSOFA**) is best used to identify patients at risk of sepsis in **out of-hospital**, **emergency** department and general hospital ward settings (less useful for ICU patients, **SOFA is better predictive for ICU**).
- Sepsis diagnosis also includes identification of a specific source or anatomic site of infection for an emergent source control.

SOFA Score



- Organ Dysfunction: Rise in SOFA of ≥ 2 points

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pa_{O_2}/FI_{O_2}, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FI_{O_2}, fraction of inspired oxygen; MAP, mean arterial pressure; Pa_{O_2}, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

❖ Old Definition of sepsis

- ✓ Sepsis = SIRS + Infection
    - SIRS = 2 out of the following 4 abnormalities
        1. Fever or hypothermia
        2. Tachycardia
        3. Tachypnea

4. Leucocytosis or leucopenia

- Infection → either of the following (i.e. confirmed or suspected infection)
  - ☛ Bacteraemia (or viraemia /fungaemia/protozoan)
  - ☛ Septic focus (abscess / cavity / tissue mass)

- ✓ Severe sepsis = Sepsis + Organ Dysfunction
- ✓ Septic Shock = Severe sepsis + Hypotension

New sepsis definition

- ❖ **Sepsis**:
  - ✓ Suspected or documented infection and
  - ✓ Acute increase of ≥2 SOFA points /a proxy for organ dysfunction/ (use ≥2 qSOFA points for emergency, non ICU case)
- ❖ **Septic Shock**: Sepsis and
  - ✓ Vasopressor therapy needed to elevate MAP ≥65 mm Hg and
  - ✓ Lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation
- ❖ Septic shock is defined as a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone
- ❖ **Severe Sepsis** → No longer used

❖ Infection related organ dysfunction:

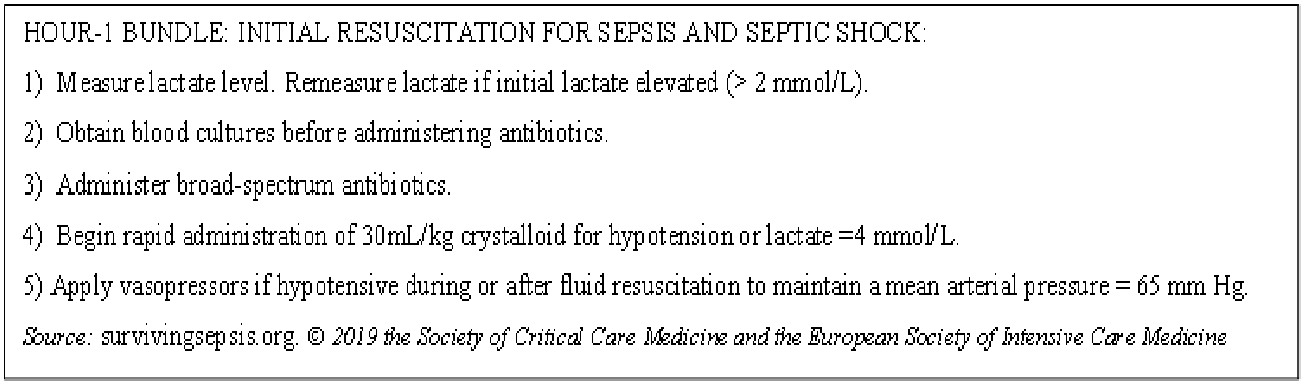
- all patients with infection should be carefully evaluated for organ failure. Conversely, any unexplained acute organ dysfunction should also raise the possibility of an underlying infection.
- Along with routine and organ specific investigations, the following are the key diagnostic recommendations for sepsis
  - ✓ Early recognition and triage
  - ✓ Measure lactate level and re-measure lactate if initial lactate is elevated (> 2 mmol/L or 18 mg/dl).
  - ✓ Obtain blood cultures
    - ☛ at least two sets of blood cultures (aerobic and anaerobic) from different sites
    - ☛ Should always be withdrawn prior to antibiotic administration as long as it does not cause a delay in administration.
    - ☛ Samples from all indwelling vascular access devices and cultures from easily accessible sites (eg, sputum, urine) are also important

- ✓ Imaging of suspected sources.
- ✓ Organ specific investigations
- ✓ Physical examination
  - ☛ BP
  - ☛ RR
  - ☛ Capillary refill

Treatment

Treatment approaches in sepsis

- ❖ Sepsis and septic shock are medical emergencies that require an immediate treatment and resuscitation.
- ❖ One of the Golden methods recommended by the surviving sepsis international guideline is a one-hour bundle (group of procedures and treatments to be carried within one hour). These are:



HOUR-1 BUNDLE: INITIAL RESUSCITATION FOR SEPSIS AND SEPTIC SHOCK:

1) Measure lactate level. Remeasure lactate if initial lactate elevated (> 2 mmol/L).
2) Obtain blood cultures before administering antibiotics.
3) Administer broad-spectrum antibiotics.
4) Begin rapid administration of 30mL/kg crystalloid for hypotension or lactate =4 mmol/L.
5) Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure = 65 mm Hg.

Source: survivingsepsis.org. © *2019 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine*

Earl measures

The following treatment stapes had better be implemented ASAP:

1) **Securing the airway** and correcting hypoxemia ASAP as indicated
2) **Secure IV line** (within 15 minutes) for the early administration of fluids and antibiotics
3) **Rapid** (or bolus) administration of **30mL/kg** IV **crystalloid** for hypotension or lactate level ≥ 4 mmol/L
   - ✓ RL or NS are preferred. Should be started within 30-60 minutes of sepsis recognition and completed within first 3 hours.
   - ✓ Can be repeated (up to 2-3 liters) until BP and tissue perfusion are acceptable, pulmonary edema follows, or there is no further response.
   - ✓ Adequacy of fluid administration can be guided by hemodynamic parameters:

- ✓ Clinical targets including MAP of 60 - 70 mmHg and UOP ≥ 0.5 mL/kg/hour.
- ✓ Dynamic measures of fluid responsiveness (eg, respiratory changes in the radial artery pulse pressure) are preferred,
- ✓ Static measures (eg, CVP 8 - 12 mmHg or central venous oxygen saturation ≥70 %).
- ✓ Initially elevated serum lactate should be followed (eg, every 6 hours), till normalization as a marker of tissue hypo-perfusion.

4) Initiation of **broad-spectrum antibiotic** within 60 minutes if possible, after blood sample withdrawal **(Table 1)**
   - o IV empiric broad spectrum (gram +ve and -ve coverage).
   - o 3rd generation cephalosporin's alone or in combination with other antibiotics can be used as first line agents in undifferentiated sepsis
   - o Select an appropriate agent based on patient's history, comorbidities, immune status, suspected site of infection, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns if available.
   - o Antimicrobial therapy in septic patients should always be initiated with a full, high end-loading dose of each agent used.
   - o **Antibiotics can be administered for a total of 10 days** in most cases. However, shorter or longer courses may be used based on the patient response, clinical condition, immunity status, specific source of septicemia, type of pathogen, etc.
   - o If suspected, add coverage against viruses and fungi (e.g. in neutropenic patients)
   - o Empiric antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (look antibiotic stewardship below)

Table 1: Antibiotic selection options for sepsis
(Community acquired with no healthcare admission in previous 90 days) and immune-competent patients.

Community acquired AND Immune-competent	**First choice antibiotic regimen**	**Second line antibiotic**
Undifferentiated (no obvious source identified)	Ceftriaxone,1 - 2g IV daily (usual dose is 1g, IV, BID)	Ampicillin, 2-4g, IV, QID plus Gentamicin, 5 mg/kg, IV, daily
Pneumonia	Ceftriaxone,1 - 2g IV daily + Azithromycin, 500mg, po, daily for 3 days add Vancomycin,1g, IV, BID if necrotizing pneumonia or high risk of MRSA suspected (if normal renal function)	Ceftriaxone + Doxycycline
UTI	Ciprofloxacin,500-600mg, po, BID or 400mg IV, BID	Ampicillin + Gentamycin
Intra-abdominal Infection	Ceftriaxone,1 - 2g IV daily + Metronidazole, 500mg, IV, TID	Augmentin or Ampicillin-Sulbactam
Skin/Skin Structure Infection — Pure cellulitis	Cefazolin, 1 - 2g, IV, TID Add Vancomycin if necrotizing abscesses or high risk of MRSA	Anti-staphylococcal penicillin's (e.g cloxacillin)
Skin/Skin Structure Infection with Special Risks *(Special Risks: immersion injuries, animal bites, diabetic foot ulcer)*	Piperacillin-Tazobactam, 4.5g, IV, TID Add Vancomycin if necrotizing abscesses or high risk of MRSA	Ampicillin-Sulbactam
Bacterial Meningitis — "Spontaneous"	Ceftriaxone,2g, IV, BID Add Vancomycin if gram positive cocci seen in CSF gram stain Add Ampicillin for age < 1 month and > 50 years/immune-compromised	Ampicillin or benzyl penicillin alone (if microorganism identified) or with gentamycin

Consecutive measures

5) Peripheral (norepinephrine) or central **inotrope infusion** therapy **for fluid refractory** septic shock during or after resuscitation.
   - ✓ Refractory are those who remain hypotensive despite adequate fluid resuscitation (eg, 3L in first three hours)
   - ✓ If indicated administered ASAP to maintain MAP ≥ 65 mm Hg.

   - ✓ Norepinephrine (**noradrenaline**) is the preferred first choice agent
     - ✓ Initial dose: **0.1 - 0.15 µg/kg/min** (8 - 12 µg/min);

       - ❖ a lower initial dose of 5 µg/minute may be used, eg, in older adults.
       - ❖ Norepinephrine must be diluted; eg, a usual concentration is 4 mg in 250 mL of D5W or NS (16 µg/mL)

- ✓ Maintenance dose: **0.025 - 0.05 µg/kg/min** (2 - 4 µg/min)
- ✓ Maximum dose rage in refractory shock: **0.5 - 0.75 µg/kg/min** (35 - 100 µg/min);

✓ If refractory to IV fluid and vasopressor

- ☛ Glucocorticoids
- ☛ inotropics and
- ☛ blood transfusions (consider RBCs if hemoglobin <7 g/dl), can be administered on an individual basis.

6) **Regular monitoring and stabilization**
   - o Be cautious with consecutive fluid administration volume in patients with CHF, ESRD and cirrhosis.
   - o If the patient respond, rate of fluid administration can be reduced or stopped, vasopressors weaned, and diuretics administered (if required)
   - o If non responsive (or failed after initial response), reinvestigate including the following considerations: removal of devices that may be infected, adequacy of antibiotic regimen, nosocomial super infections etc.
   - o Fluids may be unhelpful or harmful when the circulation is no longer fluid responsive. Hence, frequent monitoring is essential for early recognition of cardiogenic and noncardiogenic pulmonary edema (ie, acute respiratory distress syndrome [ARDS]).
7) **Source control** (emergently or at leases within 6 to 12 hours)
   - o Consider in all patients with sepsis, if the source is not identified and addressed in the initial evaluation (**Table 2**).
   - o Remove of intravascular access devices promptly if it is a possible source of sepsis or septic shock after other vascular access established.

Table 2: Source control methods for common ICU infections

Source	Interventions
Pneumonia	Chest physiotherapy, suctioning
Urinary tract	Drainage of abscesses, relief of obstruction, removal or changing of infected catheters
Catheter-related bacteremia	Removal of catheter
Peritonitis	Resection, repair, or diversion of ongoing sources of contamination, drainage of abscesses, debridement of necrotic tissue
Pancreatic infection	Drainage or debridement
Soft tissue infection	Debridement of necrotic tissue and drainage of discrete abscesses
Septic arthritis	Joint drainage and debridement
Endocarditis	Valve replacement
Prosthetic device infection	Device removal
Empyema	Drainage, decortication
Sinusitis	Surgical decompression of the sinuses

Cholangitis	Bile duct decompression

8. **Antibiotic stewardship.**
    - Sorting out the source of infection (preferably identifying the specific pathogen) and optimizing antibiotic use is critical.
    - De-escalation should be planned within 72 hours based on the culture report and other criteria's. Procalcitonin may help to guide the de-escalation and deciding on the duration.

Prevention

- Vaccination
- Proper hand washing and other peculiar precautions
- Maintaining a clean environment
- Preventing aspiration etc.

Special population considerations

Pregnant:

- ✓ Same principles as outlined in this topic can be used while aware of hemodynamics alterations during pregnancy. Readers are also encouraged to consult other up-to-date recommendations.

Elderly:

- ✓ elderly patients are more likely to have an altered clinical presentation. In addition, the severity of the disease, sensitivity to treatment and mortality is high in them, practitioners are encouraged to have more frequent monitoring schedules for this group of population.

Additional considerations

Adequate antibiotic dosing and sepsis

- ✓ Loading dose is warranted for antibiotics with low volume of distribution (teicoplanin, vancomycin, colistin) in all critically ill patients to rapidly achieve target drug concentrations. For sepsis and septic shock, an IV loading dose of 25—30 mg/kg (based on actual body weight) is suggested to rapidly achieve the target trough drug concentration. In septic patients loading doses are also important for β-lactams administered as continuous or extended infusions. Loading dose of any antimicrobial agent can be safely administered in an altered renal function, although this may affect frequency of administration and/or total daily dose. Hence appropriate dose adjustment should be performed for kidney failure with a particular attention for nephrotoxic antibiotics like vancomycin and gentamycin.

- ✓ In addition antibiotic dosing should be carefully considered based on the nature of the drug for septic patients. For instance for time dependent drugs like piperacillin/tazobactam 3.375 g every 6 hours doing schedule is better than 4.5 g every 8 hours for at least achieving a higher T > MIC. On the contrary drugs like floroquinolones and aminoglycosides will be good if given at higher doses.
- ✓ Please consult the principles of antimicrobial therapy for drugs selections and considerations for allergic reactions.

Vasopressors for sepsis

- ✓ Vasopressor infusions are high-risk medications requiring caution to prevent a medication error and patient harm. Centers should have available protocols that include steps on how to prepare and administer vasopressor infusions using a limited number of standardized concentrations. For further details and alternative vasopressors look for the management of shock under the emergency conditions

Corticosteroids for sepsis

- ✓ No septic patient should be on corticosteroids unless there is a refractory shock. IV hydrocortisone alone can be used to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability. 200mg/day IV hydrocortisone can be initiated and tapered after shock reversal was noted.

other aspects of care for patients with sepsis and septic shock like

- ✓ the use of blood products
- ✓ mechanical ventilation
- ✓ sedation and analgesia
- ✓ glucose control
- ✓ renal replacement therapy
- ✓ venous thromboembolism prophylaxis
- ✓ stress ulcer prophylaxis
- ✓ nutrition.

3.12.6 Thyrotoxicosis and Thyroid storm (የሚረጭ እንቅርት)

Thyrotoxicosis

- Thyrotoxicosis and hyperthyroidism are two different pathogenetic mechanisms which can be distinguished by the findings on the 24-hour radioactive iodine uptake **(RAIU).**
  - **Thyrotoxicosis** → Biochemical/physiological **manifestation** of excessive quantities thyroid hormone
  - **Hyperthyroidism** → **Overproduction of thyroid hormone** by thyroid gland
- Thyrotoxicosis is a condition resulting from an excess of thyroid hormones.
- If left untreated, significant weight loss and cardiac complications, including Heart Failure, may occur.
- Causes
  - Grave's disease (autoimmune, common in females)
  - Toxic multinodular goiter
  - Toxic adenoma
  - Thyroiditis (causes transient thyrotoxicosis which progresses to normal or hypothyroid state later)
  - Iatrogenic causes (side effect of medications containing iodine e.g. amidarone)

Clinical features

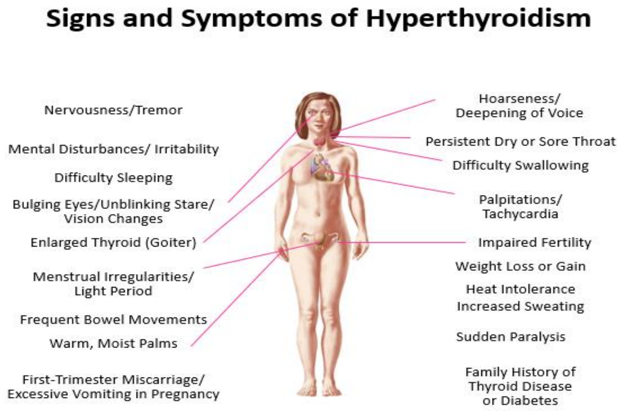
Symptoms

- Weight loss despite increased appetite
- Excessive sweating
- Heat intolerance
- Palpitations
- Nervousness and irritability
- Menstrual irregularity, mainly oligomenorrhea
- Increased hair loss
- In thyroiditis there could be neck pain and

Signs

- Tachycardia with or without irregularity: Sinus tachycardia or atrial fibrillation
- High blood pressure
- Goiter often present but not always
- Smooth and diffuse goiter in Grave's disease
- Irregular goiter in toxic multi-nodular goiter
- Single thyroid nodule in toxic adenoma

- Thyroiditis: there could be tenderness
- Tremors and brisk deep tendon reflexes
- Moist palms
- Exophthalmos (Staring or protruding eye, lid lad/retraction in Grave's disease)


Signs and Symptoms of Hyperthyroidism

Nervousness/Tremor
Mental Disturbances/ Irritability
Difficulty Sleeping
Bulging Eyes/Unblinking Stare/ Vision Changes
Enlarged Thyroid (Goiter)
Menstrual Irregularities/ Light Period
Frequent Bowel Movements
Warm, Moist Palms
First-Trimester Miscarriage/ Excessive Vomiting in Pregnancy
Hoarseness/ Deepening of Voice
Persistent Dry or Sore Throat
Difficulty Swallowing
Palpitations/ Tachycardia
Impaired Fertility
Weight Loss or Gain
Heat Intolerance
Increased Sweating
Sudden Paralysis
Family History of Thyroid Disease or Diabetes

Investigations and diagnosis

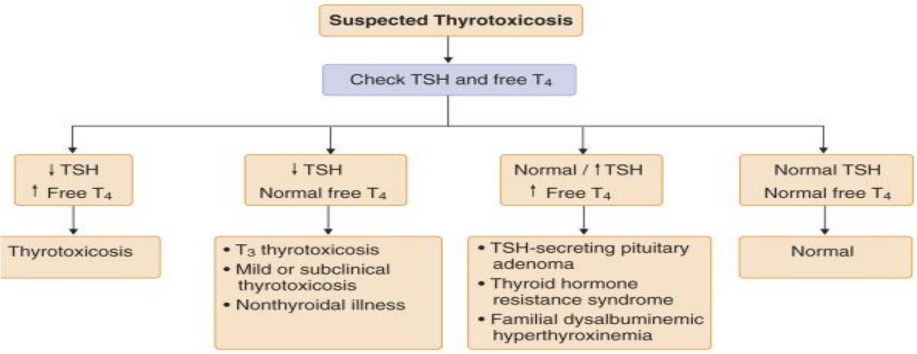
TFT

- ✓ 1^{st} determine TSH, then free T4 if TSH is abnormal
- ✓ TSH is the best initial diagnostic test. If the TSH is low, it suggests hyperthyroidism
- ✓ A low TSH result should be followed by Free T4 and total T3 determinations. Rarely Free T3 determination may be needed.
  - TSH normal = excludes hyperthyroidism
  - TSH is low and high Free T4 or T3 = Primary hyperthyroidism
  - If TSH is low, Free T4 and T3 normal= subclinical hyperthyroidism

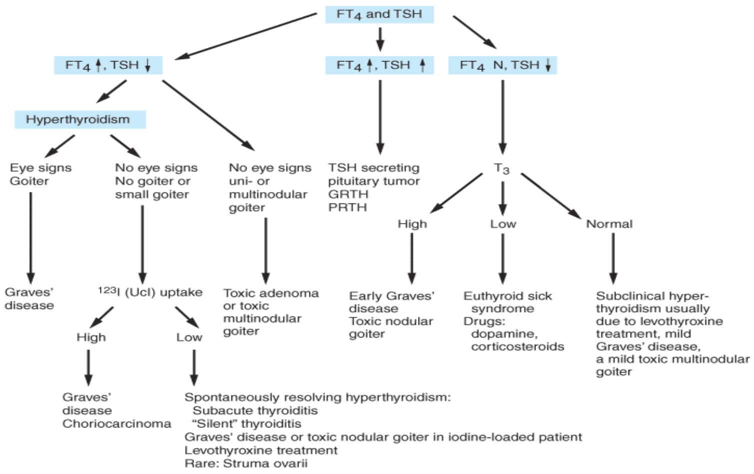
ECG

Thyroid imaging and cytology are not generally necessary in the work up of hyperthyroidism.

Algorism; Diagnosis of Hyperthyroidism


Suspected Thyrotoxicosis
Check TSH and free T4
↓ TSH ↑ Free T4
↓ TSH Normal free T4
Normal / ↑ TSH ↑ Free T4
Normal TSH Normal free T4
Thyrotoxicosis
• T3 thyrotoxicosis • Mild or subclinical thyrotoxicosis • Nonthyroidal illness
• TSH-secreting pituitary adenoma • Thyroid hormone resistance syndrome • Familial dysalbuminemic hyperthyroxinemia
Normal

Algorism; Laboratory tests in the differential diagnosis of hyperthyroidism


FT4 and TSH
FT4 ↑, TSH ↓
FT4 ↑, TSH ↑
FT4 N, TSH ↓
Hyperthyroidism
Eye signs
Goiter
No eye signs
No goiter or small goiter
No eye signs
uni- or multinodular goiter
TSH secreting pituitary tumor
GRTH
PRTH
T3
High
Low
Normal
Graves' disease
123I (UcI) uptake
Toxic adenoma or toxic multinodular goiter
Early Graves' disease
Toxic nodular goiter
Euthyroid sick syndrome
Drugs: dopamine, corticosteroids
Subclinical hyperthyroidism usually due to levothyroxine treatment, mild Graves' disease, a mild toxic multinodular goiter
High
Low
Graves' disease
Choriocarcinoma
Spontaneously resolving hyperthyroidism:
Subacute thyroiditis
"Silent" thyroiditis
Graves' disease or toxic nodular goiter in iodine-loaded patient
Levothyroxine treatment
Rare: Struma ovarii

Treatment

- ✓ Avoid stimulants e.g. Caffeine

Hyperthyroidism treatment includes;

- ❖ Ablative therapy
- ❖ Surgery → Partial thyroidectomy; should only be done after a state of euthyroid state is achieved with medical therapy
- ❖ Radioactive iodine
- ❖ Medical therapy
- ❖ Antithyroid drugs (Thionamides)

Anti-thyroid drugs (thionamide)

First line[20]

- ✓ **Propylthiouracil (PTU)**
  - o Initial dose: 100 - 150mg, PO, TID
  - o Max; 300mg, PO, TID
  - o Maintenance dose: Variable but commonly 100-200mg/day

Second line /alternative

- ✓ **Carbimazole**
  - o Initial dose 30-40mg/day divided in 2-3 doses
  - o Maximum dose 60mg/day
  - o Maintenance dose: variable but commonly 5-15mg/day
  - o Titrated down the dose based on thyroid function tests:

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[20] according to UpToDate 2018, PTU is favored over methimazole because of PTU's effect to decrease T4-to-T3 conversion. 2020 STG for general hospitals of Ethiopia, consider methimazole as first line and PTU as an alternative.

  - In the initial few months based on Free T4 levels and T3
  - After the first few months follow up is based on TSH

- **Duration of treatment** with anti-thyroid drugs
- Depends on the specific cause of the hyperthyroidism
- **In Grave's disease**: hyperthyroidism generally resolves in 1.5 - 2 years; hence, if euthyroid state is achieved the anti-thyroid drug needs to be discontinued in 1.5 to 2 years.
- **In toxic multinodular goiter**[21] **or toxic adenoma**: treatment should continue until thyroidectomy or radioiodine therapy is done

Adjunct pharmacologic treatment

Beta blockers: for symptom control until euthyroid state is achieved.

- ✓ Propranolol, 20-40mg, PO, BID or TID OR
- ✓ Atenolol 25-100mg, PO, daily OR
- ✓ Metoprolol 25-100mg, PO, daily or in two divided doses

N.B

- **Propranolol has additional effects of blocking peripheral conversion of T4 to T3**
- **Betablockers are absolutely contraindicated** in patients with;
  - Asthma or COPD
  - Severe peripheral vascular disease
  - Bradycardia
  - 2nd or 3rd degree heart block
  - Hypoglycemia-prone diabetics in whom the early warning symptoms of hypoglycemia may be masked and
  - Raynaud phenomenon
- **In the absence of contraindications, beta blockers can be administered as soon as the diagnosis of hyperthyroidism is made, even before obtaining a definitive diagnosis as to the etiology of the thyrotoxicosis.**

3.12.6.1 Thyroid storm / thyrotoxic crisis

- It is a Severe and life-threatening thyrotoxicosis with an exaggeration of the usual symptoms of hyperthyroidism

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[21] if thyrotoxicosis is associated with goiter (e.g. toxic multinodular goiter) or if you suspect thyroid malignancy, consult or link to surgery.

- An endocrine emergency with mortality rate of, as high as, 10 to 30% despite treatment.
- Usually occurs as a result of previously unrecognized or poorly treated hyperthyroidism
- Thyroid hormone levels do not help to differentiate between uncomplicated hyperthyroidism and thyroid storm. i.e. **the degree of hyperthyroidism is not a criterion for diagnosing thyroid storm.**

Precipitants

- Infection
- Trauma
- DKA
- MI
- CVA
- PE
- Surgery
- Labor
- Withdrawal of thyroid medication
- Iodine administration
- Palpation of thyroid gland
- Ingestion of thyroid hormone
- Unknown etiology (20-25%)

Clinical features

- **Exaggeration of the usual symptoms of hyperthyroidism**
- The **most common signs** are **fever**, **tachycardia out of proportion to the fever, altered mental status, and diaphoresis**
- Clues include a history of hyperthyroidism, exophthalmoses, widened pulse pressure and a palpable goiter
- Cardiovascular features include;
  - ✓ Tachycardia (>140 beats/minute) and/or atrial fibrillation → in >60 % of cases
  - ✓ CHF features.
  - ✓ Hypotension
  - ✓ Cardiac arrhythmia
  - ✓ Sudden cardiac death may occur
- Common GI symptoms include diarrhea and hyper defecation
- CNS manifestations include; Agitation, anxiety, delirium, psychosis, stupor, or coma

- ❖ Apathetic thyrotoxicosis is a distinct presentation seen in the elderly
  - ✓ Characteristic symptoms include lethargy, slowed mentation, and apathetic facies
  - ✓ Goiter, weight loss, and proximal muscle weakness also present

Diagnosis

- Thyroid storm is a **clinical diagnosis** based upon the presence of severe and life-threatening symptoms (hyperpyrexia, cardiovascular dysfunction, altered mentation) in a patient with biochemical evidence of hyperthyroidism (elevation of free T4 and/or T3 and suppression of TSH). **And treated empirically**
- There are **no universally accepted criteria** or validated clinical tools **for diagnosing** thyroid storm
- **Scoring system for thyroid storm** → In 1993, Burch and Wartofsky introduced a scoring system using precise clinical criteria for the identification of thyroid storm **(table below)**

A. **A score of ≥ 45 or more is highly suggestive** of thyroid storm
B. **a score < 25** makes thyroid storm **unlikely.**
C. A score of 25 to 44 is suggestive of impending storm.
D. While this scoring system is **likely sensitive, it is not very specific.**

Table; Diagnostic criteria for thyroid storm*

Clinical Features			**Score**
Temperature (^{0}C)	37.2 to 37.7		5
	37.8 to 38.2		10
	38.3 to 38.8		15
	38.9 to 39.4		20
	39.5 to 39.9		25
	>40.0		30
CNS effects	**Mild** → Agitation		10
	Moderate → Delirium, Psychosis, Extreme lethargy		20
	Severe → seizure, coma		30
Gastrointestinal-hepatic dysfunction	**Moderate** → Diarrhea, Nausea/vomiting, Abdominal pain		10
	Severe → Unexplained jaundice		20
CVS dysfunction	**Tachycardia**	99 to 109	5
		110 to 119	10
		120 to 129	15
		130 to 139	20
		≥140	

	Atrial fibrillation		10
	Heart failure	Mild → **Pedal edema**	5
		Moderate → **Bibasilar rales**	10
		Severe → **Pulmonary edema**	15
Precipitant history	Negative		0
	Positive		10
* A score of 45 or more is highly suggestive of thyroid storm, a score of 25 to 44 supports the diagnosis, and a score below 25 makes thyroid storm unlikely.			

Laboratory findings

TFT

- **All patients with overt primary hyperthyroidism have low TSH and high free T4 and/or T3**
- **TSH should be assessed** in all patients in whom there is A **clinical suspicion of thyroid storm;**

A. hyperpyrexia with temperature > 39.4°C
B. Goiter
C. Cardiovascular dysfunction
D. Altered mentation
E. Atrial fibrillation
F. History of antithyroid drug therapy for hyperthyroidism
G. Recent thyroid or nonthyroidal surgery
H. Recent exposure to iodine-containing contrast.

- **If the TSH is below normal, free T4 and T3 should be measured.**
- The degree of hyperthyroidism (elevation of T4 and/or T3 and suppression of TSH) in patients with thyroid storm is, in general, comparable with that in patients with uncomplicated overt hyperthyroidism. Thus, **the degree of hyperthyroidism is not a criterion for diagnosing thyroid storm.**

- **Other nonspecific** laboratory findings may include;
- Mild hyperglycemia → secondary to a catecholamine-induced inhibition of insulin release and increased glycogenolysis
- Mild hypercalcemia → may occur due to hemoconcentration and enhanced bone resorption
- Abnormal LFT → elevated transaminase and elevated bilirubin
- Leukocytosis, or leukopenia.
- **ECG** features of arrythmia

- **Radioiodine uptake is not necessary** for the diagnosis of thyroid storm, and treatment should not be delayed for scanning in patients with clinical manifestations of thyroid storm.

Management of thyroid storm

- Needs ICU care!!
- Treatment can then be divided into 5 areas:
- **Principles of treatment**
  - ✓ **General supportive care**
  - ✓ **Beta blocker** → to control the symptoms and signs induced by increased adrenergic tone
  - ✓ **Thionamide (PTU, Methimazole)** → to block new hormone synthesis
  - ✓ **Iodine solution** → to block the release of thyroid hormone
    - The administration of iodine **should be delayed for at least one hour after thionamide administration** to prevent the iodine from being used as substrate for new hormone synthesis.
  - ✓ **Glucocorticoids** → to reduce T4-to-T3 conversion, promote vasomotor stability, and possibly treat an associated relative adrenal insufficiency
  - ✓ **Identification and treatment of precipitating events**

- Iodinated radiocontrast agent (if available) → to inhibit the peripheral conversion of T4 to T3
- Bile acid sequestrants → may also be of benefit in severe cases to decrease enterohepatic recycling of thyroid hormones

A. Cholestyramine, 4 g, PO, QID

A) **General supportive care**

- ABC of life (airway protection, oxygenation, fluids and cardiac monitoring)
- Proper fluid, electrolyte, and nutritional support.
  - Many patients require substantial amounts of fluid, while others may require diuresis because of CHF
- Antipyretics
  - Cooling blanket
  - **PCM,** 1g, PO, TID/QID
  - Avoid **Aspirin** (Salicylates)!! → because it can increase serum free T4 and T3 concentrations by interfering with their protein binding (i.e. displace T4 from TBG /Thyroid binding globulin/)
- ± Phenobarbital (sedation)…↑peripheral metabolism; inactivation of T_4, T_3.

- **Prevent peripheral effects:**

B-Blocker

A) **Propranolol**, 60 - 80 mg, PO, every 4 - 6 hours, with appropriate adjustment for heart rate and blood pressure. OR

- ✓ IV: 0.5 to 1 mg administered over 10 minutes followed by 1 to 3 mg over 10 to 15 minutes every several hours with continuous cardiac monitoring; when transitioning to oral therapy, IV therapy may need to be continued until the effects of oral therapy are achieved

B) **Atenolol,** 25 to 100 mg, PO, once or twice daily; up to 200 mg/day OR

C) **Metoprolol;** Immediate release (**metoprolol tartrate): 25 to 50 mg, PO, BID or TID** OR

- ✓ may also consider administering once-daily extended-release formulation (**metoprolol succinate)**

D) **Esmolol** (IV), 500 µg/kg IV bolus, then 50-200 µg/kg/min maintenance

N.B

- **Propranolol has the additional effects of blocking peripheral conversion of T4 to T3. But,** this effect of propranolol is slow, occurring over 7 to 10 days, and contributes little to the therapeutic effects of the drug
- Look at contraindications of betablockers from thyrotoxicosis section above.

- **Decrease de novo synthesis:**
  - **PTU,** 600-1000mg PO stat, followed by 200-250 mg, PO, q4 hrs OR
  - Methimazole, 40 mg, PO stat, then 20 mg PO, every 4 - 6 hours

    - **PTU is favored over methimazole because of PTU's effect to decrease T4-to-T3 conversio**

- **Iodine solutions to prevent release of hormone → One hour** after **the first dose of thionamide is taken.**
  - ✓ **Lugol solution (**Potassium iodide and iodine), 8 - 10 drops (1ml = 20drops), PO, TID/QID or
  - ✓ **Saturated solution of Potassium iodide** (SSKI), 5 drops PO, QID or

- **Glucocorticoids**
  - ✓ Hydrocortisone, 100 mg, IV, TID or
  - ✓ Dexamethasone, 2 mg, IV, QID

- **Identification and treatment of precipitating events**
  - ✓ **Diuretics and digitalis** for heart failure

- ✓ Broad spectrum **antibiotics** for infection
- ✓ Others → look at precipitant factors above

✍ **If the patient continues to deteriorate** despite appropriate therapy circulating thyroid hormone may be removed by **plasma transfusion, plasmapheresis, charcoal plasma perfusion**

3.12.7 Hypothyroidism

- ❖ The body requires thyroid hormones for normal metabolism and growth.
- ❖ Hypothyroidism is a condition in which there is a reduction in thyroid hormone production.
- ❖ In adults, it may be the cause of a slow metabolic rate, systemic problems and dementia.
- ❖ The most common reason is decreased production by thyroid glands (called primary hypothyroidism), rarely it could be caused by pituitary abnormalities (secondary)
- ❖ Antibody-related thyroid gland destruction, surgical removal of the thyroid, pituitary lesions or surgery, congenital, severe iodine deficiency are the major causes.
- ❖ Myxedema coma describes the most severe state of hypothyroidism and is a medical emergency.

Types of Hypothyroidism

Primary hypothyroidism

- ❖ From thyroid destruction

Central or secondary hypothyroidism

- ❖ From deficient TSH secretion, generally due to sellar lesions such as pituitary tumor or craniopharyngioma
- ❖ Infrequently is congenital

Tertiary hypothyroidism

- ❖ From deficient TSH stimulation above level of pituitary→ i.e. lesions of pituitary stalk or hypothalamus
- ❖ Is much less common than secondary hypothyroidism

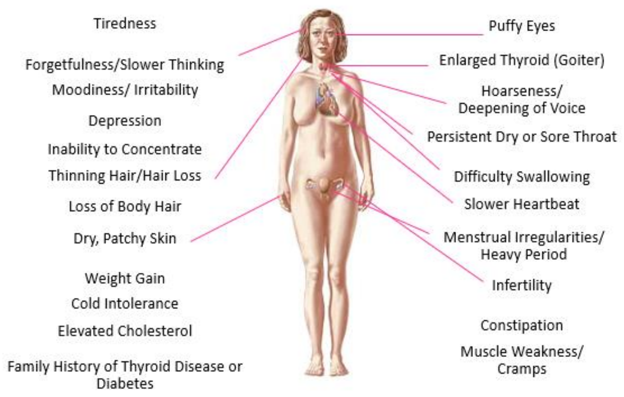
Clinical features

Symptoms

- ❖ Patients could remain asymptomatic for several years or they might not recognize the symptoms themselves.
- ❖ Intolerance to cold environments, constipation, weight gain, hair loss, dry skin
- ❖ Hoarse voice, lethargy, memory loss, depressed reflexes, dementia
- ❖ Abnormal menstrual periods and sub-fertility (in adult females)

Signs

- Puffy face, pallor, slow pulse (usually <60 per minute)
- Goiter may be present



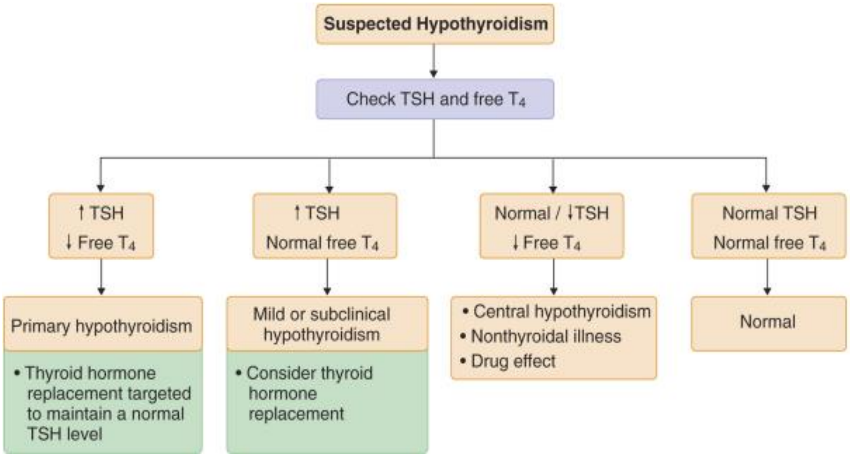
Clinical Features of Hypothyroidism

Tiredness
Forgetfulness/Slower Thinking
Moodiness/ Irritability
Depression
Inability to Concentrate
Thinning Hair/Hair Loss
Loss of Body Hair
Dry, Patchy Skin
Weight Gain
Cold Intolerance
Elevated Cholesterol
Family History of Thyroid Disease or Diabetes
Puffy Eyes
Enlarged Thyroid (Goiter)
Hoarseness/ Deepening of Voice
Persistent Dry or Sore Throat
Difficulty Swallowing
Slower Heartbeat
Menstrual Irregularities/ Heavy Period
Infertility
Constipation
Muscle Weakness/ Cramps

Investigation and Diagnosis

- TSH
- Free T4

- The diagnosis of hypothyroidism is usually delayed due to lack of recognition.
- A very high index of suspicion should be maintained in any adult woman who presented with fatigue or non-specific symptoms.
- TSH is the best screening test
  - ✓ TSH >20 micro unit/ml: highly suggestive primary hypothyroidism
  - ✓ Normal TSH: excludes primary hypothyroidism
  - ✓ Mildly elevated TSH (<20 microunits/ml): needs freeT4 determination
  - ✓ Mildly elevated TSH with normal free T4: subclinical hypothyroidism


Suspected Hypothyroidism
Check TSH and free T4
↑TSH ↓Free T4
↑TSH Normal free T4
Normal / ↓TSH ↓Free T4
Normal TSH Normal free T4
Primary hypothyroidism
• Thyroid hormone replacement targeted to maintain a normal TSH level
Mild or subclinical hypothyroidism
• Consider thyroid hormone replacement
• Central hypothyroidism
• Nonthyroidal illness
• Drug effect
Normal

Treatment

Levothyroxine

- Starting dose → for patients with no cardiovascular disease
  - for patients with no cardiovascular disease
    - Young patients → 100 µg/day
    - Elderly patients → 50 µg/day
  - Patients with established cardiac disease → 25-50 µg/day
- Dose adjustment
  - Dose adjustment should be made after at least 2-3 months of therapy
  - Dose increments by 25-50 µg/day in 2- 3months
  - Achieving TSH is the target of treatments
  - After normalization of TSH, annual follow up of TSH suffices

Myxedema Coma

- Myxedema is a rare life-threatening decompensation of hypothyroidism
- Usually in individuals with long-standing hypothyroidism
- Most often seen in the winter months
- It is an endocrine emergency with Mortality rate of > 50%
- Occurs in patients (esp. Elderly women) who have severe, untreated hypothyroidism, and although it may be spontaneous

Precipitating factors

- Infection
- Surgery or trauma
- Myocardial infarction
- Stroke
- exposure to cold
- drugs → use of sedatives or opiates, Lithium, Amiodarone

Clinical features

- Onset is insidious, with progressive stupor culminating in coma.
- In addition to the clinical features of hypothyroidism patients may present with

A. Hypothermia
B. Seizures
C. Altered metal status → Coma, delusions, and psychosis (myxedema maddness)
D. Hyponatremia → Dilutional secondary to decreased free-water clearance
E. Hypoglycemia → Secondary to impaired gluconeogenesis
F. Hypotension
G. Bradycardia
H. Respiratory Failure → Secondary to decreased strength of respiratory muscle, Hypercapnia and hypoxia is common

Investigations and Diagnosis

High clinical suspicion, commonly has Hx. of hypothyroidism
RBS → Hypoglycemia
CBC → Anemia, leukocytosis suggests underlying infection as precipitant
Serum electrolyte → Hyponatremia
Liver enzymes → ↑ Transaminases
ECG → Sinus Bradycardia, Prolonged QT interval, Low voltage, Flattened or inverted T waves
Others → ↑ CPK, ↑ LDH, ↓Po2 and ↑PCo2 on ABG's

Treatment

- Admit to ICU for ventilatory support and for intravenous medications.
- **Supportive measures**

A. ABC of life
B. Passive rewarming (heating blanket)
C. Correction of hyponatremia → Hyponatremia typically responds to fluid restrictions. Severe cases may require hypertonic saline with Lasix
D. Dextrose-containing IV fluids if there is hypoglycemia
E. Vasopressors are usually ineffective and should only be used in severe hypotension
F. Empiric antibiotics for infection.
G. Avoid exposure to potent sedative or analgesic agents that may exacerbate altered mental status

- **Parenteral thyroxine**:

A. **Levothyroxine** 300-500 µg, IV, slowly followed by 50-100 µg daily

Alternative

B. L-triiodothyronine 25 µg IV/PO, TID (12.5 µg in patients with cardiovascular disease)

- **Glucocorticoids** → if there is concomitant adrenal insufficiency

A. Hydrocortisone 100 mg IV, TID

- **Precipitating causes** should be sought and treated

3.12.8 VTE (DVT and PTE)

Dr. Mulualem. G, Dr. Robel. D

- Venous thromboembolic disease (VTE) refers thrombosis (blood clot) that occurs in the deep veins, called deep vein thrombosis (DVT), or embolization in to pulmonary arterial circulation called pulmonary embolism (PE).
- One of the common sites for thrombus formation in the deep veins of the legs or pelvis. This is known as deep vein thrombosis, or DVT.
- The thrombus can dislodge and travel in the blood, particularly to the pulmonary arteries. This is known as pulmonary embolism, or PE.
- The term 'VTE' includes both DVT and PE.
- VTE covers a spectrum ranging from asymptomatic calf vein thrombosis to symptomatic DVT or PE.
- Pulmonary embolism can fatal, if it is not detected and treated early.
- Non-fatal VTE can cause serious long-term complications

Risk factors for VTE

- Immobility
- Previous VTE
- Major surgery, e.g. orthopedic, abdominal and pelvic surgery
- Trauma → especially involving the pelvis and lower limbs
- Pregnancy and postpartum state
- Contraceptive pill use, hormone replacement therapy (HRT)
- Cancer
- Obesity
- Medical conditions such as;

A. Heart Failure
B. Nephrotic syndrome or CKD
C. HTN
D. COPD
E. SLE
F. IBD

- Inherited disorders causing hypercoagulability

Pathogenesis

- A major theory described the pathogenesis of **VTE** is called **Virchow's triad**, which occurs as a result of: mnemonic → EBC
  - ✓ Endothelial Injury
  - ✓ Blood flow alterations (Stasis)
  - ✓ Coagulopathy → Alterations in the Constituents of Blood

Clinical features

- **VTE** mimics other illnesses, and **PE** is known as "*the Great Masquerader*," making diagnosis difficult.
- **Occult PE** is especially hard to detect when it occurs concomitantly with overt *Heart Failure* or *Pneumonia.*
- In evaluating patients with **possible VTE**, the initial task is to decide on the **clinical likelihood** of the disorder.
- **VTE** can cause death from **PE** or, among survivors, Chronic Thromboembolic Pulmonary Hypertension and Post thrombotic Syndrome/chronic venous insufficiency/may occur.

DVT

- For patients who have **DVT,** the most common history is
  - ✓ A **cramp** in the lower calf that persists for several days and becomes more uncomfortable as time progresses.
- Physical findings, if present at all, may consist only of mild palpation discomfort in the lower calf.
- **Massive DVT** is much easier to recognize.
  - ✓ The patient presents with **marked thigh swelling and tenderness** during palpation of the common femoral vein.
  - ✓ **In extreme cases**, patients are **unable to walk** or may require a cane, crutches, or a walker.

PE

- For patients who have **PE,** the most common history is **unexplained breathlessness.**
  - ✓ **Dyspnea is the most common symptom** of PE, and **Tachypnea is the most common sign.**
- Dyspnea, Syncope, Hypotension, or Cyanosis indicates a **Massive PE**, Whereas Pleuritic Pain, Cough, or Hemoptysis often suggests a **Small Embolism** situated distally near the pleura.
- On **physical examination,**
  - ✓ Young and previously healthy individuals may appear anxious
  - ✓ But otherwise seem well, even with an anatomically large PE.
- The presence of pulmonary infarction usually indicates a small PE
  - ✓ But one that is exquisitely painful because it lodges peripherally, near the innervation of pleural nerves.
- Pleuritic Chest Pain is more common with small, peripheral emboli. However, larger, more central PEs can occur concomitantly with peripheral pulmonary infarction.

- They may have dyspnea only with moderate exertion.
- They often lack "classic" signs such as
  - ✓ Tachycardia, Low-grade Fever, Neck Vein Distention, and an Accentuated Pulmonic Component of S2.
- Sometimes **paradoxical bradycardia** occurs.

Investigations and diagnosis

- Routine laboratory tests for baseline (e.g. CBC, LFT, coagulation studies)

A. But they are not useful diagnostically.

- Imaging Modalities include:

A. **Compressive Ultrasonography** (with Doppler)

- Diagnostic test of choice
- Sensitivity and specificity of > 95% for the diagnosis of DVT.
- However, about 50% of patients with PE have no imaging evidence of DVT on U/
- Features of venous thrombosis on Compressive U/S:

A) Lack of Compressibility
B) Direct thrombus visualization
C) Abnormal Doppler flow

B. MR Venography (contrast enhanced)
C. Chest CT(CTPA)

- Supportive Investigative modalities include;

A. Cardiac biomarkers
B. CXR
C. ECG.
D. Echo
E. D- dimers

- D dimers are a breakdown of Fibrin by Plasmin. The normal level is < 500(negative result).
- Elevation of D-dimer indicates endogenous although often clinically Ineffective thrombolysis.
- The Sensitivity of the D-dimer is >80% for DVT (Including Isolated Calf DVT) and >95% for PE
- But are not specific are more applicable for ‘ruling out’ VTE.

Classification

- Patients with **Massive PE** present with

A. Systemic Arterial Hypotension and
B. Usually have anatomically widespread thromboembolism.

- Those with **Sub massive PE** have

A. RV hypokinesis on Echocardiography but
B. Normal Systemic Arterial Pressure.

- Patients with **Low risk PE** have both

A. Normal right heart function and
B. Normal systemic arterial pressure.

- They have an excellent prognosis with adequate anticoagulation.

Modified Wells score

- In evaluating patients with possible VTE, the initial task is to decide the clinical likelihood of the condition.
- There are different clinical criteria to determine the probability of VTE (Pretest Probability) of which Wells Score is commonly used.
- The modified Wells score **classifies** patients suspected of having VTE into two levels as **'Likely' and 'Unlikely'**

Pretest probability of deep vein thrombosis (Wells score)

Clinical feature	Score
Active cancer (treatment ongoing or within the previous six months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than three days or major surgery, within four weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
Score	
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less
Modification:	
This clinical model has been modified to take one other clinical feature into account: a previously documented deep vein thrombosis (DVT) is given the score of 1. Using this modified scoring system, DVT is either likely or unlikely, as follows:	
DVT likely	2 or greater
DVT unlikely	1 or less

Interpretations and actions to be done in Wells score *(for best setup, not applicable in our setup)*

DVT likely (Wells score ≥ 2 points):

- do a proximal leg vein ultrasound scan, with the result available within 4 hours if possible
- If scan is positive, start mx for DVT.
- If initial scan is negative or if it's impossible to get scan results in 4 hours, do a D-dimer test and start interim therapeutic anticoagulation.
- If scan is negative and D dimer is positive, stop interim anticoagulation and offer a repeat scan at 6-8 days
- If both scan and D dimer are negative, look for other potential ddx
- If the scan is positive, continue anticoagulation

DVT is unlikely (Wells score ≤ 1 point), offer a D dimer test.

- If the D-dimer test result is negative, think about other differentials
- If the D-dimer test result is positive, offer a proximal leg vein ultrasound scan, with the result available within 4 hours if possible or interim therapeutic anticoagulation, and a proximal leg vein ultrasound scan with the result available within 24 hours.
- If the proximal leg vein ultrasound scan is positive, continue management for DVT
- If the proximal leg vein ultrasound scan is negative, look for other differentials.

PE Likely (Wells score > 4 points):

- offer a computed tomography pulmonary angiogram (CTPA) immediately
- If CTPA is positive, start anticoagulation
- If CTPA is negative but DVT is still suspected, do CUS
- If CTPA is negative and DVT is not suspected, look for another differential

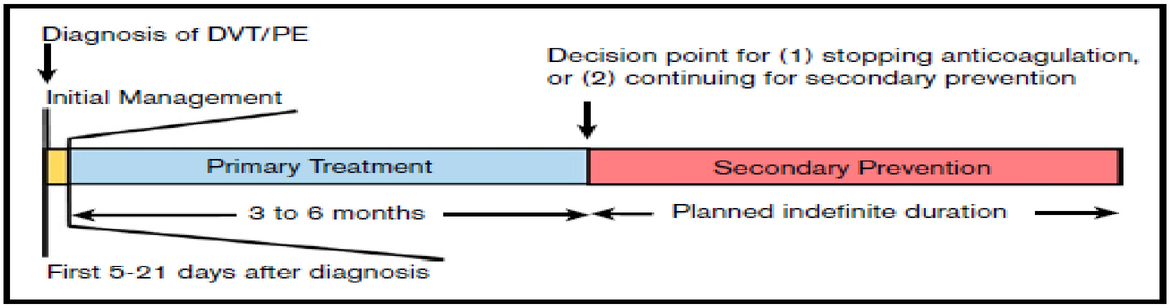
PE Unlikely (Wells score ≤ 4 points):

- offer a D-dimer test with the result available within 4 hours if possible
- if the D-dimer test result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation while awaiting the result
- If the D-dimer test result is positive, continue mx for PE
- If the D dimer result is negative stop interim therapeutic anticoagulation think about alternative diagnoses.

Management of VTE

- The management of VTE is done in three different phases:

A. Initial Management
B. Primary Treatment
C. Secondary prevention


Diagnosis of DVT/PE
Initial Management
Decision point for (1) stopping anticoagulation, or (2) continuing for secondary prevention
Primary Treatment
Secondary Prevention
3 to 6 months
Planned indefinite duration
First 5-21 days after diagnosis

I. **Initial management** (first 5-21days)

- aim is to prevent thrombus extension, embolization and bleeding.
- The main modality of mgt is anticoagulation.
- Choice of agents:

A. LMWH
B. Fondaparinux
C. Direct Oral Anticoagulants (rivaroxaban, apixaban)
D. UFH

II. **Primary treatment** (3-6 months)

- refers to the minimal length of time initial venous thromboembolism should be treated.

III. **Secondary prevention** (Indefinite)

- long term anticoagulation with the intent to prevent VTE recurrence.

Non pharmacologic management

- Elastic compression stockings after anticoagulation
- Early ambulation after proper anticoagulation

Pharmacologic

I. Acute treatment

First line

- ✓ UFH, 5000 Units, IV, bolus; then 250 Units/Kg/dose, Sc, BID or 17,500 Units SC, BID (for an average adult) until two consecutive INR values become therapeutic (2-3) or
- ✓ Enoxaparin 1mg/kg, SC, BID, until two consecutive INR values become therapeutic (2-3)
  - Enoxaparin dose should be **reduced or** it should be **avoided** in patients with **advanced CKD** (GFR<30ml/min)

  PLUS
- ✓ Warfarin (starting simultaneously with heparin)
  - Starting dose: 5 mg, P.O., daily with regular dose adjustment and monitoring of INR until target of 2 - 3 is attained.
  - Add warfarin 5mg, PO, on day 1 or 2 of UFH, daily for 2 days, check INR after 2 days and adjust based on the result
  - Overlap warfarin and UFH for at least 5 days until desired INR/INR=2-3/ maintained for 24hr then discontinue UFH.

N.B

- **The full effect of warfarin requires at least 5 days,** even if the prothrombin time, used for monitoring, becomes elevated more rapidly.
- **If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis.**
- Overlapping UFH or LMWH with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

Alternatives

- ✓ Rivaroxaban 15mg PO BID X 3 weeks
  - Rivaroxaban should be avoided in patients with advanced CKD (GFR<30ml/min)

Management of warfarin-associated bleeding or supratherapeutic INR

(See the table below)

❖ At least half of the bleeding complications with warfarin occur When the INR exceeds the therapeutic range (which is 2 to 3).

INR >9 without bleeding

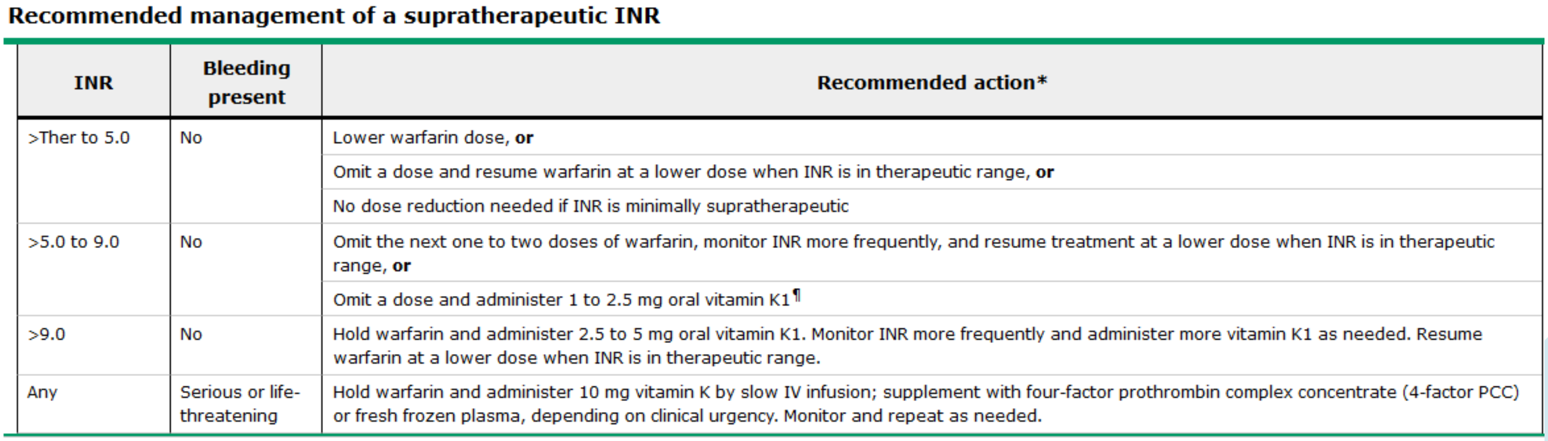
- warfarin therapy should be held and give **oral vitamin K, 2.5 to 5 mg**
- Nonbleeding patients should not be given PCC or FFP solely to correct a supratherapeutic INR, as these products have associated risks.
- The **INR is monitored daily or every other day**, and **warfarin is resumed at a lower dose once the INR in the therapeutic range.**

INR 5 to 9 without bleeding

- warfarin is held temporarily (e.g. one or two doses) with or without administration of a small dose of oral vitamin K (e.g. 1 to 2.5 mg).
- Warfarin generally is resumed at a lower dose once the INR is in the therapeutic range.

INR <5 without bleeding

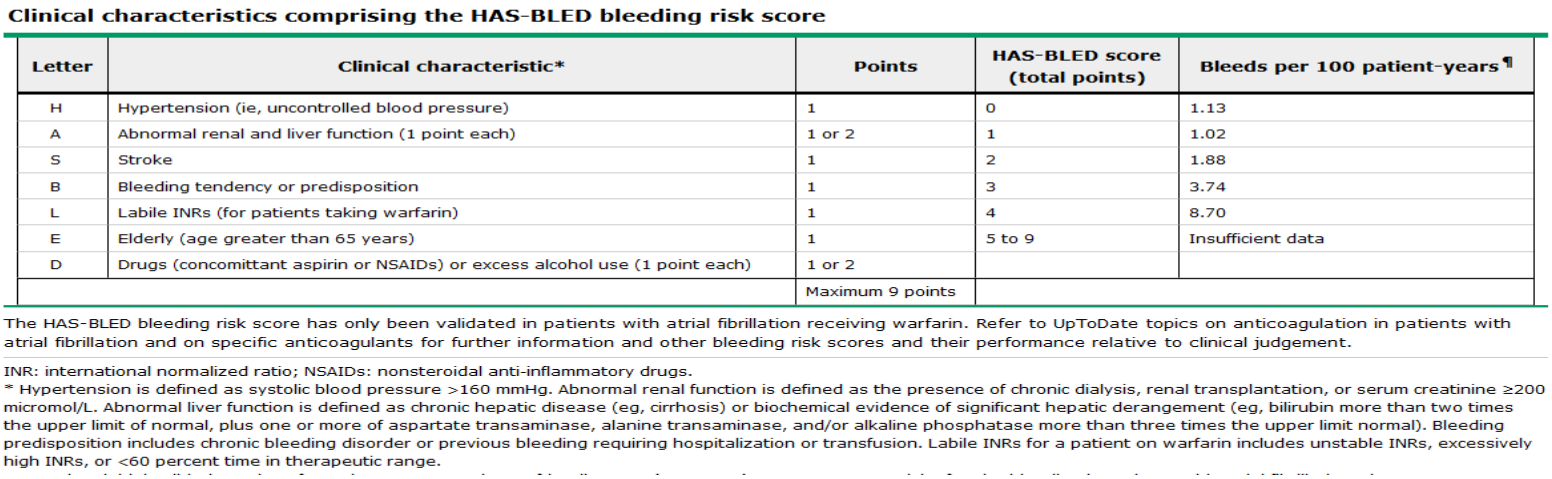
- One or more doses of warfarin may be omitted and/or the dose is reduced slightly.
- If the INR elevation is minimal and/or expected to be transient, no dose reduction may be necessary.
- Additional therapies such as vitamin K are not indicated in this setting.



Recommended management of a supratherapeutic INR

INR	Bleeding present	Recommended action*
>Ther to 5.0	No	Lower warfarin dose, **or**
		Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, **or**
		No dose reduction needed if INR is minimally supratherapeutic
>5.0 to 9.0	No	Omit the next one to two doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, **or**
		Omit a dose and administer 1 to 2.5 mg oral vitamin K1¶
>9.0	No	Hold warfarin and administer 2.5 to 5 mg oral vitamin K1. Monitor INR more frequently and administer more vitamin K1 as needed. Resume warfarin at a lower dose when INR is in therapeutic range.
Any	Serious or life-threatening	Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with four-factor prothrombin complex concentrate (4-factor PCC) or fresh frozen plasma, depending on clinical urgency. Monitor and repeat as needed.

HAS-BLED bleeding risk score, in patients with atrial fibrillation receiving warfarin



Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points	HAS-BLED score (total points)	Bleeds per 100 patient-years¶
H	Hypertension (ie, uncontrolled blood pressure)	1	0	1.13
A	Abnormal renal and liver function (1 point each)	1 or 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding tendency or predisposition	1	3	3.74
L	Labile INRs (for patients taking warfarin)	1	4	8.70
E	Elderly (age greater than 65 years)	1	5 to 9	Insufficient data
D	Drugs (concomittant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2		
		Maximum 9 points		

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarin. Refer to UpToDate topics on anticoagulation in patients with atrial fibrillation and on specific anticoagulants for further information and other bleeding risk scores and their performance relative to clinical judgement.

INR: international normalized ratio; NSAIDs: nonsteroidal anti-inflammatory drugs.

* Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal renal function is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than two times the upper limit of normal, plus one or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than three times the upper limit normal). Bleeding predisposition includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion. Labile INRs for a patient on warfarin includes unstable INRs, excessively high INRs, or <60 percent time in therapeutic range.

II. Chronic treatment

- Warfarin, dose adjusted to achieve target INR of 2 -3 OR
- Rivaroxaban 20mg po, daily.

III. Duration of anticoagulation

- Patients with VTE due to a reversible/time-limited risk factor (e.g. surgery): **3-6 months.**
- Patients with first episode of idiopathic/unprovoked VTE: 3-6 months
- Most patients with advanced malignancy should be treated **indefinitely** or until the cancer resolve
- Patients with recurrent idiopathic/unprovoked VTE: indefinitely

Management of VTE in special population

1. Pregnancy:

- Adjusted-dose subcutaneous **LMW heparin** is the **preferred agent** for initial and long-term anticoagulation in pregnant women with acute DVT.
- **UFH is alternatives** to LMW heparin.
- **Warfarin can cause embryopathy** when administered between 6 and 12 weeks.

A. Cancer:

- **Treatment of DVT is associated with higher morbidity**, due to higher than usual rates of both recurrent thrombosis and anticoagulant-associated bleeding.
- **LMWHs are the preferred agents** for the anticoagulation in those with preserved renal function.

3.12.8.1 VTE prophylaxis

- VTE is a major cause of death and mortality among patients admitted for both surgery and acute medical care.
- The major risk factors that predispose patients for the development of VTE are well known.
- Provision of prophylaxis for hospitalized patients who are at high risk of VTE is an established strategy which decreases death and morbidity.
- The major risk of pharmacologic prophylaxis with anticoagulants or antiplatelets is increased risk of bleeding; hence, the risk of bleeding should also be assessed along with assessment for the risk of VTE.

VTE prophylaxis in surgical patients

- Risk assessment for VTE in surgical patients mainly depends on the type of surgery and the bleeding risk associated with the procedure.

Type of surgery	Need for VTE prophylaxis	Recommended thromboprophylaxis	Duration
Major orthopedic surgery	Yes	First line Enoxaparin 40mg, Sc, daily Or Rivaroxaban 10mg, po/day Second line UFH, 5,000 IU SC, BID	2-4 weeks Starting 12 hours after surgery
Major general surgery	Yes	Enoxaparin (same dose as above) Or UFH (same dose as above)	2-4 weeks
Major neurosurgery	No		
Laparoscopic cholecystectomy	No		
Transurethral prostatectomy or radical prostatectomy	No		
Cardiac or vascular surgery	Yes	Enoxaparin (same dose as above) Or UFH (same dose as above)	
Major trauma	Yes		
Major gynecologic	Yes		

VTE prophylaxis in medical patients

- The major risk factors for VTE among medical patients hospitalized for acute care

A. ICU admission (critical care),
B. Stroke with lower limb paralysis
C. Active cancer
D. Known thrombophilia (inherited or acquired)
E. Prolonged immobilization ≥ 3days
F. Heart failure
G. Acute respiratory failure
H. Sepsis
I. Chronic inflammatory diseases.

- The presence of one or more risk factors puts the patient at increased risk.
- The higher the number of the risk factors, the higher the risk of developing VTE.
- Although not widely validated, there are a few risk assessment models designed to help clinicians make a better risk assessment and decide on the provision of prophylaxis.
- We the use of one of the risk assessments tools: IMPROVE-VTE risk assessment model (see the table below).
- Before starting prophylactic anticoagulation assessment of the risk of bleeding is as important as assessing the risk of VTE. Use the IMPROVE-VTE bleeding risk assessment tool given below.
- The major **contraindications for pharmacologic prophylaxis**

A. Active bleeding
B. Intracranial hemorrhage of any cause
C. Thrombocytopenia (<50,000 or <100,000 with additional risk factor)
D. Major surgery planned in the coming 12 hours.

- If a patient has a high risk of bleeding based on clinical evaluation or using the IMPROVE VTE bleeding risk assessment, prophylactic anticoagulation should be avoided.
- **Options for pharmacologic prophylaxis**

A. Enoxaparin 40mg, SC, daily for the time of hospitalization during acute illness OR
B. UFH, 5,000 IU, SC, BID for the time of hospitalization during acute illness 3 - 4 weeks

Table. IMPROVE VTE risk assessment model

No.	Risk factors at admission	Points
	Known thrombophilia	3
	Previous VTE	3

	Malignancy (Active or treated in the last 6 months)	1
	Current lower limb paralysis	2
	Immobility ≥ 7 days	1
	Age >60 years	1
	ICU stay	1
Score 0-1 = low risk, no need for prophylaxis Score 2 -3 = moderate risk, needs prophylaxis Score > 4 = High risk, needs prophylaxis Any score 2 or above = Needs for prophylaxis		

Table: IMPROVE VTE Bleeding risk assessment		
No.	**Risk factor**	**Score**
	Active GI bleeding	4.5
	Bleeding in the past three months before admission	4
	Platelet count <50,000	4
	Age ≥ 85	3.5
	Hepatic failure (INR>1.5)	2.5
	Severe Renal Failure (GFR <30ml/min)	2.5
	Liver failure (INR>1.5)	2.5
	Any ICU admission	2.5
	Central venous catheter	2
	Rheumatic disease	2
	Active cancer	2
	Age 40-84	1
	Male	1
	Moderate renal failure (GFR 30-59ml/min)	1
A score >7 is considered high risk for bleeding		

3.12.9 Tetanus (መንጋጋ ቆልፍ)

Dr. Mulualem. G, Dr. Robel. D

- Tetanus is a toxin-mediated disease of the nervous system characterized by muscle spasms.
- Caused by *Clostridium tetani*. - anerobic spore-forming bacilli found in the soil
- Usually follows trauma.
- Four forms:
  - ✓ Generalized (the most common)
  - ✓ Local
  - ✓ Cephalic
  - ✓ Neonatal
- *C. tetani* does not grow in healthy tissues
- Factors that increase chance of tetanus disease are:

- ✓ Penetrating injuries
- ✓ Superinfection by other bacteria
- ✓ Devitalized tissue
- ✓ Foreign body presence
- ✓ Tissue ischemia

- ➢ Clinical situations that may also predispose for tetanus:
  - ✓ Infected umbilical stump in neonates
  - ✓ Septic abortion
  - ✓ Unhygienic circumcision
  - ✓ Dental infections
  - ✓ Infected diabetic foot ulcers
- ➢ In 10% of tetanus patients site of entry is not identified

Clinical Features

- ➢ Incubation period:
  - ✓ Ranges from a few days to a few weeks with an average of a week
  - ✓ A short incubation period (time from injury to first symptom) of ≤4 days generally indicates severe disease.
  - ✓ The period between the first symptom and the development of muscular spasms is termed the period of onset. Shorter periods of onset, particularly <48hrs, are again associated with more severe forms of tetanus
  - ✓ Shorter in neonatal tetanus and with injuries close to the CNS
- ➢ Recovery from tetanus takes 4-6 weeks
- ➢ **Generalized tetanus**
  - ✓ The commonest form
  - ✓ The most common and important clinical features include **trismus (lockjaw)** localized or generalized muscular rigidity and spasm.
  - ✓ Lockjaw (or trismus) the cardinal symptom is characterized by: intense, painful spasms of the masseter muscles, and an inability to open the mouth
  - ✓ **Other symptoms:** stiff neck, opisthotonos, risus sardonicus, board abdomen, apnea during spasms, dysphagia, sweating, arrhythmia, fever, labile BP
  - ✓ Consciousness is not impaired in tetanus patients
  - ✓ The presence of arrhythmia, extreme oscillation in blood pressure, diaphoresis, laryngeal spasm and urinary retention may suggest autonomic dysfunction.
- ➢ **Local tetanus**
  - ✓ Rare
  - ✓ Signs/ symptoms limited to one part of the body
  - ✓ Difficult to diagnose early
  - ✓ Less severe

  - ✓ Often evolves to generalized form
- **Cephalic tetanus**
  - ✓ Head and neck area
  - ✓ Often evolves to generalized form
  - ✓ Dysphagia, trismus, focal cranial neuropathies
  - ✓ CN-VII is commonly affected, but others (CN — III, IV, VI and XII) may be affected alone or in combination
- **Neonatal tetanus**
  - ✓ Neonates of unimmunized or poorly immunized mothers
  - ✓ Follows unclean management of the umbilical stump
  - ✓ Intense cry, refusal to feed, poor sucking, difficulty opening mouth due to trismus, facial muscle spasms, rigid body parts

Investigations

- Clinical, based on the history and examination findings.

Severity Scoring

- There are several severity scores used but the Ablett classification has been used most commonly.

Table; Ablett classification of severity of Tetanus	
Grading	**Clinical features**
I- Mild	Mild to moderate trismus; general spasticity; no respiratory embarrassment; no spasm; little or no dysphagia
II- Moderate	Moderate trismus; well-marked rigidity; mild to moderate but short spasms; moderate respiratory embarrasement with RR greater than 30; mild dysphagia
III-Severe	Severe trismus; generalized spasticity; reflex prolonged spasms; increased RR greater than 40; apnoeic spells; severe dysphagia; tachycardia greater than 120.
IV-Very Severe	Grade III and violent autonomic disturbances involving the cardiovascular system. Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent.

Treatment

Non pharmacologic

- Admit patients to a quiet place, and in severe cases, to an ICU if possible for continuous cardio-pulmonary monitoring.
- Wound care which includes thorough cleansing and debridement.
- Intubation or tracheostomy, and mechanical ventilation in severe cases.
- Adequate hydration and feeding should be given attention

Pharmacologic

- Patients with severe tetanus should be managed in the intensive care setting where mechanical ventilator and appropriate medication are available. This may necessitate referral of most patients to specialized centers.

A. Control of spasm

- **Diazepam**, 10 mg I.V. every 4 hourly
  - ✓ the dose being titrated depending on the response.
  - ✓ Large doses as much as 250mg daily could be used.
  - ✓ NB: Heavy sedation with higher doses of diazepam has a potential to cause respiratory depression and should only be used while the patient is mechanically ventilated.

  PLUS
- **Chlorpromazine**, 25-50mg I.M. QID alternated with diazepam

  PLUS
- **Magnesium sulphate**, loading dose of 40mg/kg IV over 30 min, followed by IV infusion of 2g/h for patients over 45kg and 1.5g/h for patients 45kg or

under.

- ✓ Magnesium is used in patients with severe tetanus for whom tracheostomy has been done; it helps in reducing the need for other muscle spasm controlling drugs and may reduce muscle spasms and well-studied in reducing autonomic instabilities)

B. **Neuromuscular blockade**

- ➢ Neuromuscular blocking agents are used when sedation alone is inadequate.
  - ✓ **Suxamethonium,** 20-100mg I.V. depending on the effect with mechanical ventilation may be employed in patients with severe laryngeal spasm
  - ✓ **Halting toxin production and neutralizing circulating toxins**
  - ✓ **Wound debridement** to eradicate spores and necrotic tissue is recommended for all patients with tetanus. This avoids ideal conditions for germination.

C. **Antimicrobial treatment**

- ➢ **Metronidazole**, 500mg I.V/PO TID or QID for 7-10 days
  - ✓ Has some benefit. In addition, antimicrobials will fail to eradicate *C. tetani* unless adequate wound debridement is carried.

alternative

- ✓ Penicillin G 2 to 4 million units IV every 4 to 6 hours for 7 to 10 days.

Metronidazole reduces the requirement for muscle relaxants and sedatives than penicillin’s and cephalosporins.

D. **Neutralization of circulating (unbound) toxin**

- ➢ **Human Tetanus immunoglobulin (**HTIG), 500 IU I.M. stat (at a different site to the vaccine)
  - ✓ the use of passive immunization to neutralize unbound toxin (bound toxin is irreversible) is considered as the standard care as it is associated with improved survival.
  - ✓ Give immediately after the diagnosis, with part of the dose infiltrated around the wound.
- ➢ **Intravenous immune globulin** may be administered as an **alternative** if HTIG is not available.

E. **Active immunization**

- ➢ **Tetanus Antitoxin (TAT)** 10,000 IU IM. after a skin test:
  - ✓ All patients with tetanus, particularly in those never immunized previously, full series of active immunization with appropriate booster doses is recommended immediately upon diagnosis, because tetanus infection do not confer immunity.
  - ✓ Administer vaccines at a different site than tetanus immune globulin.

F. **Control of Autonomic dysfunction**

- **Hypertension and supra-ventricular tachycardia** can be treated with combined **alpha and Beta- blockers**.
  - ✓ **Labetalol** is widely used first line option.
  - ✓ Beta blockers alone (e.g. propranolol had caused a sudden death) are not recommended.
  - ✓ **Morphine** (0.5-1.0mg/kg per hour) can also be used to control the sympathetic hyperactivity.

Table; summary of Drugs for Tetanus management		
Drug name	**dose**	**Comment**
Control of spasm		
Diazepam	10 mg I.V. should be given every 4 hourly, the dose being titrated depending on the response.	Be cautious with respiratory depression at high dose, if not mechanically ventilated.
Neuromuscular blockade		
Suxamethonium	20-100mg I.V.	May be employed in patients with severe laryngeal spasm.
Control of autonomic dysfunction		
Magnesium sulphate	Load 40mg/kg IV over 30 min, then IV infusion of 2g/h for > 45kg & 1.5g/h for ≤45kg	well-studied in reducing autonomic instabilities; help to reduce spasms
Labetolol	0.25-1.0mg/min IV infusion	Alpha and beta blocker, avoid beta blockers alone
Morphine	0.5-1.0mg/kg per hour	
Halting toxin production and neutralizing circulating toxins		
Wound debridement to eradicate spores and necrotic tissue	Initially and as necessary	Halt bacteria germination and related toxin production
Human Tetanus immunoglobulin (HTG)	500 IU I.M. single dose	Start immediately. Help to neutralize unbound circulating toxins
Tetanus Antitoxin (TAT)	10,000 IU IM.	Start immediately. after a skin test or history taking

Airway and other supportive measures

- If ICU services are not available, acute respiratory failure is a principal cause of death from tetanus.
- In the absence of an ICU
  - ✓ A separate ward or room should be designated for patients with tetanus, and
  - ✓ Keep sensory stimuli to a minimum because loud noises, physical contact, and light can trigger tetanic spasms. Eye shades and ear plugs can also be used to reduce stimuli.
  - ✓ Nondepolarizing neuromuscular blockers (e.g. vecuronium and pancuronium) are not safe in the absence of ventilatory support. Yet, benzodiazepines and baclofen can be used with careful doses titration to avoid respiratory depression. Magnesium sulfate can be used to adjunctive muscle spasm.
- Supportive care is the basic treatment for tetanus because the tetanus toxin once bound to neurons cannot be displaced from the nervous system. Hence patients with severe cases will remain immobile for a long (for weeks), most of them in mechanical ventilation. As a result, **they are predisposed to decubitus ulcers, nosocomial infections, thromboembolic disease, tracheal stenosis, and gastrointestinal hemorrhage.**
- Bed sore prevention measures are important
- Early nutritional support may be required, enteral feeding is preferred, to meet the increasing energy demands of tetanus patients.
- Prophylactic acid blockers or sucralfate may prevent gastroesophageal hemorrhage from stress ulcer.
- Thromboembolism prophylaxis with heparin, or low molecular weight heparin should be administered early.
- Physical therapy should be started as soon as spasms have ceased, to avoid disability from prolonged muscle wasting and contractures.

Prevention

- Appropriate tetanus prophylaxis (human tetanus immune globulin and/or vaccine (e.g. TT)) should be administered ASAP following a wound as well as up one to two weeks of injury for previously vaccinated (not fully vaccinated or vaccinated before 5-10 years) and up to 21 days of injury for previously unvaccinated late care seekers.
- This is because the incubation period is quite variable; most cases occur within 8 days, but the incubation period can be as short as 3 days or as long as 21 days.
- For previously unvaccinated or partially vaccinated a human tetanus immune globulin is concurrently (with the vaccine) recommended unlike the full vaccinated individuals.
- Immunization of pregnant or childbearing age women reduces neonatal tetanus mortality by more than 90 %.
- Improving hygiene during home births is also help to prevent neonatal tetanus.

3.12.10 Leprosy (የስጋ ደዌ በሽታ ፣ ቁምጥና)

Dr. Asmare. W

Leprosy (Hansen's disease)

- A Chronic, granulomatous infection and its sequelae caused by Mycobacterium leprae, principally affecting the Skin & peripheral nerves.
  - ✓ But also the Eyes, Testes, the mucosa of the upper respiratory tract, Lymph nodes, small muscles & bones of face, hands, & feet are affected. (but capable of affecting any tissue or organ.)
  - ✓ Acute inflammatory episodes called leprosy reactions occur at any time during which Nerve Damage occurs.
- The major disability is due to Nerve Damage to Autonomic, Sensory and Motor fibers of the peripheral nerves of hands & feet.
- Blindness and facial disfigurement results from direct involvement of eyes, face by the bacilli and/or secondary to cranial nerves.
- **Prompt diagnosis and treatment** helps to avoid most complications of leprosy.
- Leprosy can cause **permanent**, and **progressive psychological**, and **physical impairment.**
- **serious social** and **economic consequences result from**
  - ✓ Distress, anxiety and functional difficulties during daily living.
  - ✓ social ostracism due to **leprosy stigma**
  - ✓ **4 - 5 million** people are disabled by leprosy world wide.

Etiology

- In 1873 Gerhard Armauer Hansen — identified M. leprae.
- Earliest description - from India

Microbiology

- **M. leprae** → acid-fast bacillus .
- A member of the family Mycobacteriacae.
- straight or slightly curved rod-shaped organism.
- Multiplies very slowly → generation time 14 days.
- An obligate intracellular parasite.
- It grows best at 27ºC to 33ºC→ predilection for affecting cooler areas of the body
  - ✓ the skin, nerve segments close to the skin, and the mucous membranes of the upper respiratory tract ……..
- M. leprae has never been cultured in **artificial media.**
- Grows in **armadillos extensively**
- Armadillo and foot pad of mouse → core body temperature of 34ºC. (M. leprae grows best at 30-33ºC)
- **It is a disease virtually confined to humans.**
- Leprosy is found in wild armadillos in the south, central United States and in Chimpanzee, Sooty Mangabey Monkeys, in Africa

Epidemiology of leprosy Ethiopia

- M :F 2:1 in case of lepromatous leprosy.
- Affects predominantly young, 15-44yrs of age.
- Long Incubation period

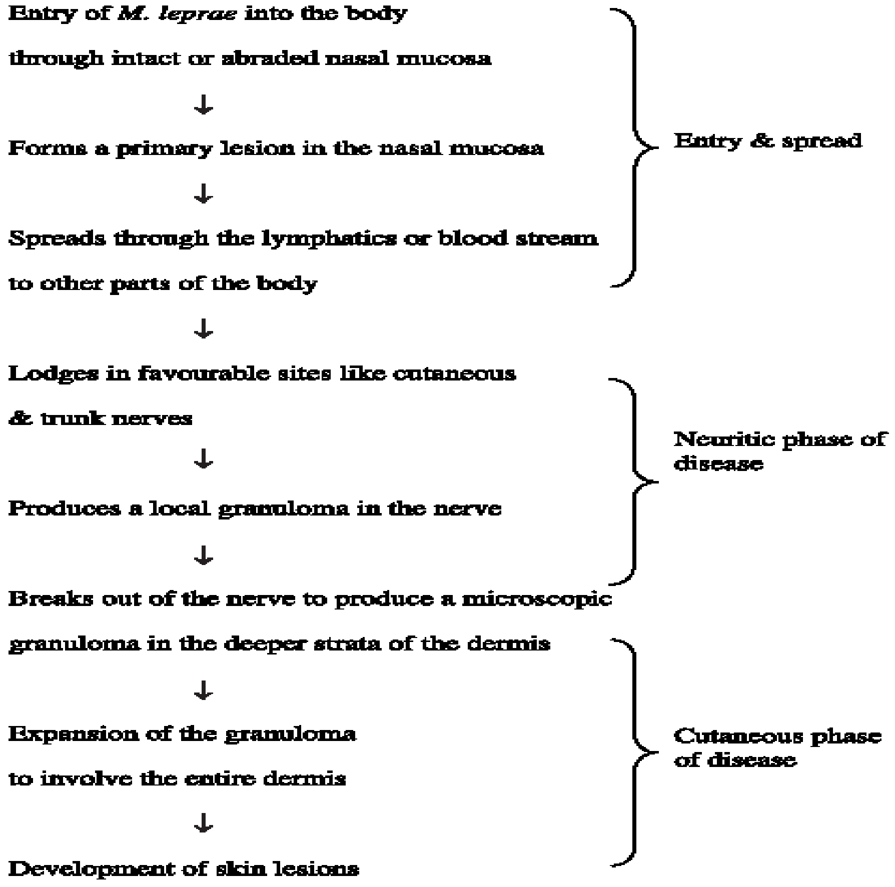
  - ✓ Tuberculoid :2-5 years
  - ✓ Lepromatous :8-12 years (~30years)
- WHO's goal of elimination is Prevalence of less than 1 case per 10,000 Population.
- In Ethiopia the average prevalence is 0.6 - 0.7
- Areas of higher prevalence have also been reported

Transmission

- uncertain.
- Nasal droplets from lepromatous patients. (believed to be the mode of transmission by most authorities)
- skin-to-skin contact — **not considered** as an important route.
- Requirements for the spread of leprosy;Contagious patient (lepromatous patient),Susceptible individual (genetic, poverty …)and Close or intimate contact.
- Contact with a tuberculoid case carries a very low risk.

Pathogenesis

- a little is known


Entry of *M. leprae* into the body through intact or abraded nasal mucosa
Forms a primary lesion in the nasal mucosa
Spreads through the lymphatics or blood stream to other parts of the body
Entry & spread
Lodges in favourable sites like cutaneous & trunk nerves
Produces a local granuloma in the nerve
Neuritic phase of disease
Breaks out of the nerve to produce a microscopic granuloma in the deeper strata of the dermis
Expansion of the granuloma to involve the entire dermis
Development of skin lesions
Cutaneous phase of disease

- A predominantly Th1 response is seen in tuberculoid leprosy patient → IL-2, IFN- γ & TNF-β → granuloma formation, mild form of the disease.

- Th2 response is seen in lepromatous patient → IL-4, IL-5, IL-10 → suppress macrophage activity and allow strong humoral response, unrestricted proliferation of M. leprae.

Classification of leprosy

- The Aim of Classification of Leprosy
  - ✓ Guide the treatment.
  - ✓ follow the disease progress and predict outcome
  - ✓ Assess the likelihood of complications.
  - ✓ Plan control measures.
  - ✓ Aid for communication between experts.
  - ✓ Research e.g. clinical trials.

  1, WHO's classification
  2, Ridley-Jopling's classification

WHO's classification

- Based on the number of skin lesions present, number of peripheral nerves involved & presence or absence of bacilli on smears.
- **Paucibacillary disease**
  - ✓ one to five skin lesions and no bacilli on smear testing.
  - ✓ if only one nerve is involved, & nerve biopsy smear is negative (in case of pure neural leprosy)
- **Multibacillary disease**
  - ✓ six or more skin lesions with or without bacilli
  - ✓ Less than six skin lesions, which have a positive slit skin smear result.
  - ✓ if ≥ 2 nerves are involved or if one or more nerve involved with positive smear (in case of pure neural leprosy)

Ridley-Jopling's classification.

- Used to differentiate types of leprosy.
- helps in determining prognosis.
- It is based on clinical picture, histology, sometimes bacillary load.
- **The granulomatous spectrum of disease described by Ridley&Jopling;**
  - ✓ Polar tuberculoid (TT)
  - ✓ Border line tuberculoid (BT)
  - ✓ Mid borderline (borderline) (BB)
  - ✓ Borderline lepromatous (BL)
  - ✓ Lepromatous leprosy (LLp)
  - ✓ **Polar tuberculoid leprosy** (TT)
- Immunity is strong.
- Solitary plaque having annular configuration, both border is sharply marginated, indurated, erythematous, scaly, hypo pigmented hypesthetic, anhidrotic.
- Size is often less than 10cm.

Borderline Tuberculoid leprosy (BT)

- Immunity is strong to restrain infection.
- Somewhat unstable (upgrade or downgrade).
  - ✓ Primary lesions could be papules or plaques.

  - ✓ Plaques may have sharply marginated satellite papules.
  - ✓ Lesions larger >10cm.
  - ✓ Multiple, asymmetric lesions are common.
  - ✓ Impaired sensation.
- ➢ Nerve trunk involvement, enlargement or palsies involving
  - ✓ Commonly not more than two nerves.

Borderline leprosy (BB)

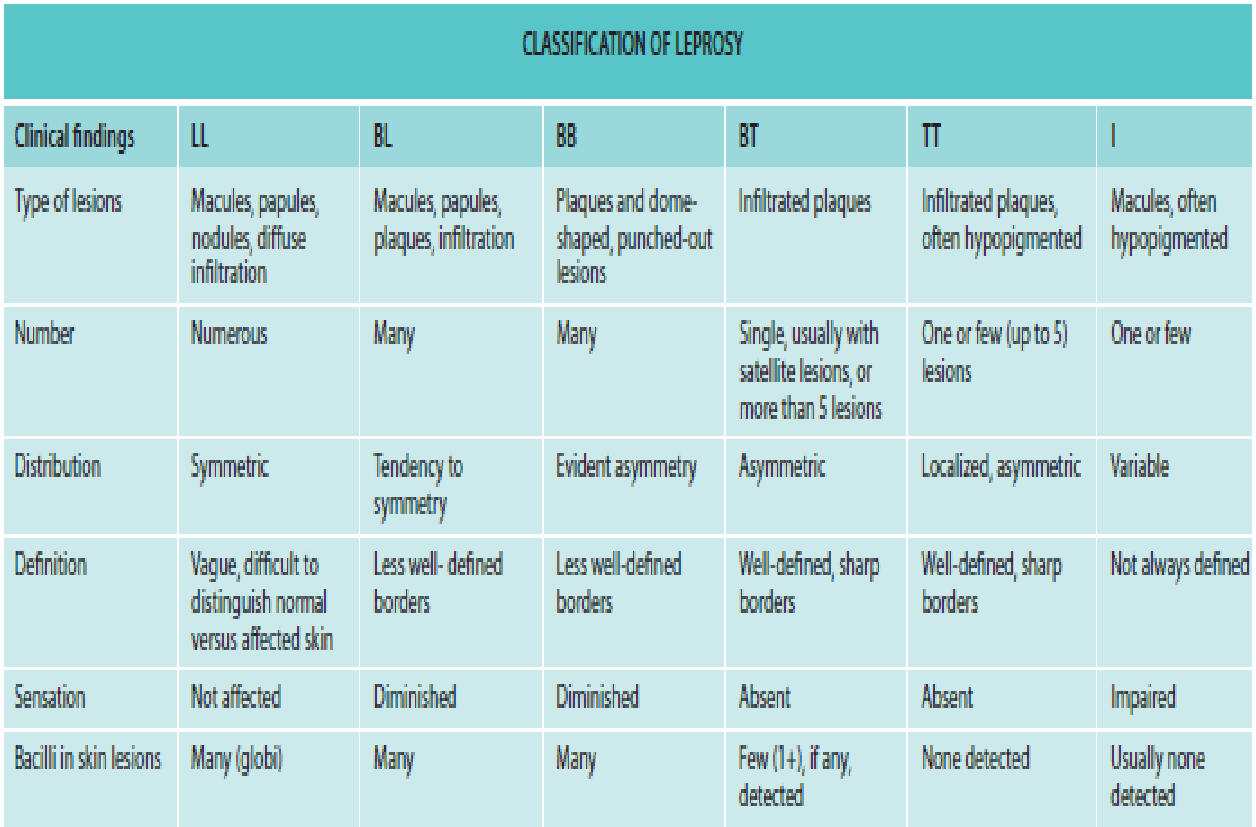
- ➢ represents mid-zone of the granulomatous spectrum.
- ➢ it is the most unstable form.
- ➢ patients quickly down grade or uprgrade
- ➢ annular lesion with sharply mariginated interior and poorly mariginated exterior marigns.
- ➢ Large plaque with islands of normal appearing skin.
- ➢ Patient are rarely seen due to the unstable nature of this form.
- ➢ Classic 'Diamorphic' lesion.

Borderline lepromatous (BL)

- ➢ **Resistance**
  - ✓ Is too low to restrain bacillary proliferation but still sufficient to induce tissue destructive inflammation (nerve damage) thus, patients with BL have the worst of both worlds.
- ➢ Highly variable in its clinical presentation.
- ➢ Diamorphic lesion can be seen in in 1/3rd of patients.
- ➢ Punched out lesions can also be seen
- ➢ Lesions range from solitary to wide spread.
- ➢ Poorly defined papules & nodules.
- ➢ Annular & plaque lesions are often asymmetric.
- ➢ Lepromatous like nodules are symmetric if numerous.
- ➢ Nerve trunk palsies have highest prevalence.

Lepromatous leprosy (LL)

- ➢ Lack of CMI → unrestricted proliferation & widely disseminated multiorgan disease.
- ➢ Poorly defined nodules are most common lesion (~2cm) with Symmetrical distribution.
- ➢ Diffuse dermal infiltration
- ➢ Thickening of ear lobes, widening of nasal root, fusiform swelling of digits, loss of lateral 1/3rd eye brows (madarosis), leonine facies.



CLASSIFICATION OF LEPROSY

Clinical findings	LL	BL	BB	BT	TT	I
Type of lesions	Macules, papules, nodules, diffuse infiltration	Macules, papules, plaques, infiltration	Plaques and dome-shaped, punched-out lesions	Infiltrated plaques	Infiltrated plaques, often hypopigmented	Macules, often hypopigmented
Number	Numerous	Many	Many	Single, usually with satellite lesions, or more than 5 lesions	One or few (up to 5) lesions	One or few
Distribution	Symmetric	Tendency to symmetry	Evident asymmetry	Asymmetric	Localized, asymmetric	Variable
Definition	Vague, difficult to distinguish normal versus affected skin	Less well- defined borders	Less well-defined borders	Well-defined, sharp borders	Well-defined, sharp borders	Not always defined
Sensation	Not affected	Diminished	Diminished	Absent	Absent	Impaired
Bacilli in skin lesions	Many (globi)	Many	Many	Few (1+), if any, detected	None detected	Usually none detected

CLINICAL MANIFESTATIONS AND DIAGNOSIS

- Leprosy should be considered in the setting of skin lesions that are chronic and not responding to standard treatment for more common conditions or when
- sensory loss is observed within lesions or in extremities.
- Additional clues include presentation of cuts or burns in the absence of pain and travel history including residence in endemic countries (foreign birth, military experience, etc).
- **90% history of numbness** first→ sometimes years before the skin lesions appear
- **Sensory loss**: **Temperature → light touch → pain → deep pressure.**
- The skin lesions appear later during the course of the disease.
- Borderline patients may present in reaction with nerve pain, sudden palsy, multiple new skin lesions, pain in the eye, or a systemic febrile illness.
- Patients commonly present with
  - ✓ skin lesions
  - ✓ weakness or numbness due to a peripheral nerve lesion
  - ✓ a burn or ulcer in an an aesthetic hand or foot.
- **Assess for physical signs in 3 general areas**:
  - ✓ **For cutaneous lesions.**
  - ✓ **Neuropathies.**
  - ✓ **Eye damage.**
- **For cutaneous lesions**
  - ✓ Assess the number, distribution, morphology, symmetry of skin lesions.

- ✓ Always look at the face, ears, trunk, buttock and lateral aspect of the limbs for cutaneous lesions.
- ✓ A hypo pigmented macule/plaque with a raised border is often the first cutaneous lesion.
- ✓ Lesions may or may not be hypo esthetic.

- ➢ **Neuropathies**
  - ✓ Assess for areas of hypoesthesia (light touch, pinprick, temperature) & anhidrosis especially of peripheral nerve trunks and cutaneous nerves.
  - ✓ commonly affected nerves include **posterior tibial nerve, ulnar, median, lateral popliteal, and facial nerves.** (assess for enlargement, tenderness, consistency, irregularities)
  - ✓ sensory loss, motor loss, and autonomic loss should be assessed.
  - ✓ Nerves commonly involved include
    - ▪ the ulnar and median (claw hand)
    - ▪ the common peroneal (foot drop)
    - ▪ the posterior tibial (claw toes and plantar insensitivity)
    - ▪ Facial, radial cutaneous,great auricular.
- ➢ **Eye damage** is most often seen with facial lesions.
  - ✓ Lagophthalmos (inability to close the eye) due to involvement of facial nerve.
  - ✓ a late finding in LL
    - ▪ reduced corneal reflex→ leaving dry eyes and reduced blinking are due to ophthalmic division of trigeminal nerve involvement. (corneal ulceration, scarring, blindness)
    - ▪ Extraocular findings include madarosis , leonine facies..

Diagnosis

- ➢ the cardinal signs of leprosy
- ➢ The diagnosis of leprosy is primarily clinical.
- ➢ Diagnosis is based on one or more of 3 signs:
  - ✓ Hypo pigmented or reddish patches with definite loss of sensation.
  - ✓ Thickened peripheral nerves with loss of sensation & or weakness of muscles supplied.
  - ✓ Acid-fast bacilli on skin smears or biopsy material.
- ➢ **Lab… Slit skin smear**
  - ✓ Lesions and cooler areas of the skin, such as the fore head, earlobes, chin, elbows, knees, buttock and trunk are preferred sites for smear.
  - ✓ An incision 5 mm long and 3 mm deep is made and blade is turned at right angles to cut, and to take fluid, and pulp from the dermis.
  - ✓ M. leprae are detected by modified Zeihl-Nelson staining.
- ➢ **Skin biopsy**
  - ✓ To assess the extent and type of infiltrate and involvement of dermal nerves, a full-thickness skin biopsy should be taken from the most active margin of the most active lesion, entirely within a lesion.
  - ✓ Skin smears, in which a small incision is made (on the ears, elbows, and/or knees) to collect a dermal fluid sample, are no longer widely used.

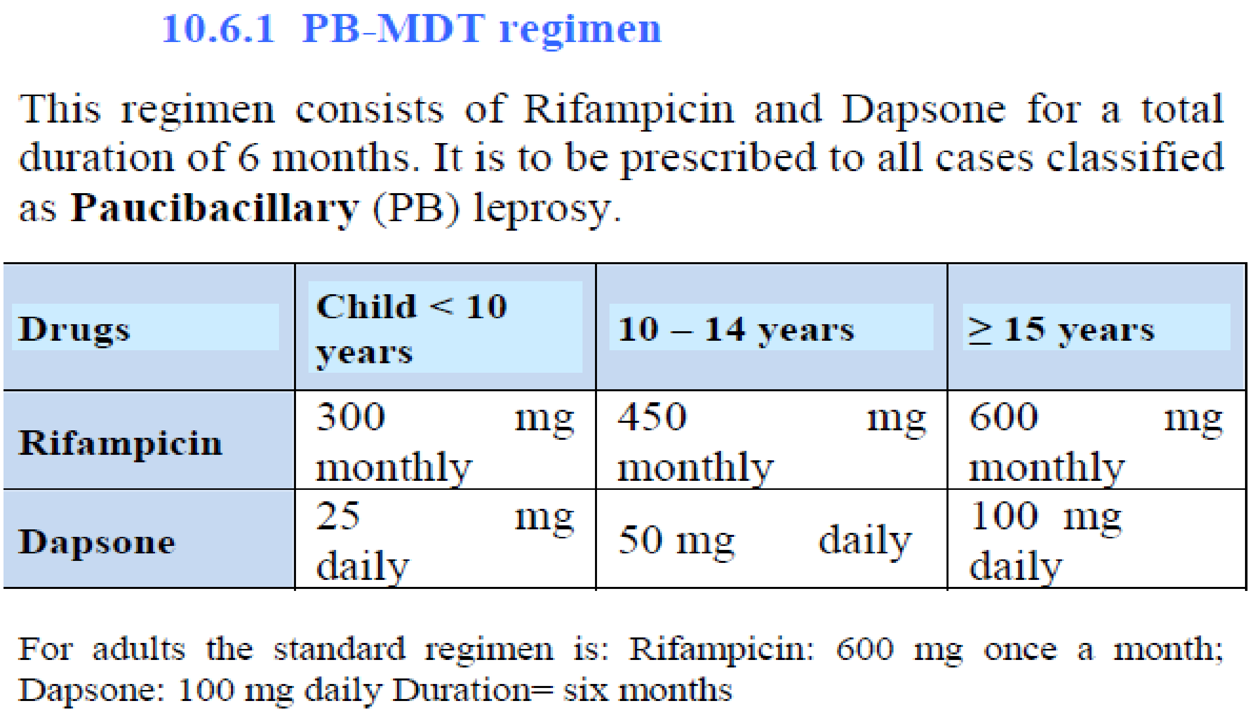
  - ✓ Mycobacterial culture should be performed on biopsies from skin lesions to exclude cutaneous infections due to *M. tuberculosis* and nontuberculous mycobacteria.
- ➢ **Polymerase chain reaction**
  - ✓ PCR is available for detection of *M. leprae* DNA in tissue.
  - ✓ PCR is more useful as an identification tool (eg, when clinical or histologic features are inconclusive) than as a detection tool.
  - ✓ In one study, PCR on biopsies from patients with lepromatous disease had sensitivity and specificity of >90 percent and 100 percent; PCR on biopsies from patients with tuberculoid disease had sensitivity and specificity of 34 and 80 percent, respectively.
  - ✓ PCR is not commercially available but can be performed by the NHDP Center.

Management

Goals

- ➢ Bacteriological cure.
- ➢ Detect and treat reactions.
- ➢ Prevent nerve damage and disabilities.
- ➢ Treat complications of nerve damage.
- ➢ Rehabilitation
  - ✓ Physical
  - ✓ Mental and
  - ✓ Social

Multi drug therapy



10.6.1 PB-MDT regimen

This regimen consists of Rifampicin and Dapsone for a total duration of 6 months. It is to be prescribed to all cases classified as **Paucibacillary** (PB) leprosy.

Drugs	**Child < 10 years**	**10 – 14 years**	**≥ 15 years**
Rifampicin	300 mg monthly	450 mg monthly	600 mg monthly
Dapsone	25 mg daily	50 mg daily	100 mg daily

For adults the standard regimen is: Rifampicin: 600 mg once a month; Dapsone: 100 mg daily Duration= six months

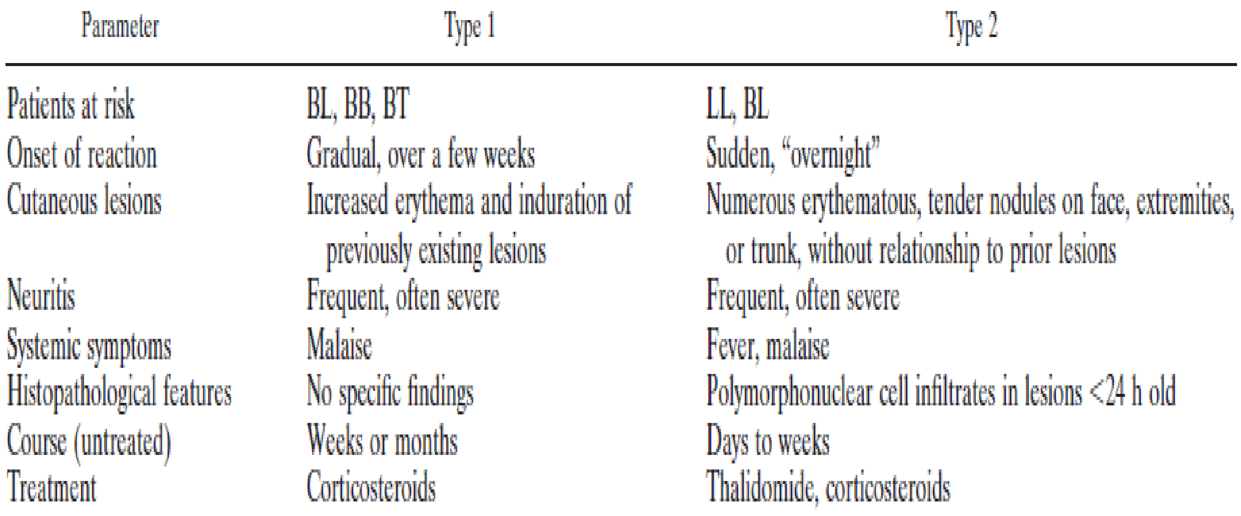
10.6.2 MB-MDT regimen

This regimen consists of Rifampicin, Dapsone and Clofazimine, for 12-month duration. It is to be prescribed to all cases classified **as Multibacillary (MB)** leprosy.

Drugs	Child < 10 years	10 – 14 years	≥ 15 years
Rifampicin	300 mg monthly	450 mg monthly	600 mg monthly
Clofazimine	100 mg monthly	150 mg monthly	300 mg monthly
Clofazimine	50 mg twice a week	50 mg every other day	50 mg daily
Dapsone	25 mg daily	50 mg daily	100 mg daily

For adults the standard regimen is: Rifampicin: 600 mg once a month, Dapsone: 100 mg daily Clofazimine: 300 mg once a month and 50 mg daily Duration= 12 months.

- Type-1 (Reversal).
- Type-2 (Erythema nodosum leprosum, ENL).



Parameter	Type 1	Type 2
Patients at risk	BL, BB, BT	LL, BL
Onset of reaction	Gradual, over a few weeks	Sudden, "overnight"
Cutaneous lesions	Increased erythema and induration of previously existing lesions	Numerous erythematous, tender nodules on face, extremities, or trunk, without relationship to prior lesions
Neuritis	Frequent, often severe	Frequent, often severe
Systemic symptoms	Malaise	Fever, malaise
Histopathological features	No specific findings	Polymorphonuclear cell infiltrates in lesions <24 h old
Course (untreated)	Weeks or months	Days to weeks
Treatment	Corticosteroids	Thalidomide, corticosteroids

Management of Type I (RR)

- ➢ General principle
  - ✓ Lab investigation
  - ✓ Grading severity of reaction into mild and sever
- ➢ **Mild**

  - ✓ inflammation of skin lesions without nerve involvement
- ➢ **Severe**
  - ✓ Reactional lesion overlying major nerves
  - ✓ Nerve involvement
  - ✓ Edema of hand and feet
  - ✓ Mild RR persisting over 4 weeks
- ➢ **Specific treatment**
  - ✓ Prednisone tapering dose starting 40 to 60 mg, depending on severity of reaction
  - ✓ Other drugs: azathopurine, cyclosporine
  - ✓ Nerve abscess: surgical release
  - ✓ Prevention of secondary disabilities by health education (eye, hand & foot care)

Type II (Erythema Nodosum Leprosum)

- ➢ Immune complex reaction due to excess production of antibody to M. leprae antigens
- ➢ Common in lepromatous spectrum (BB, BL & LL)
- ➢ Panniculitis and vasculitis (tender subcutaneous nodules)
- ➢ Mild to moderate inflammation of nerves
- ➢ Generalized systemic manifestation

Treatment of ENL

- ➢ **General**
- ➢ Lab investigation
- ➢ Grading of severity
- ➢ Mild
  - ✓ Skin eruption without nerve tenderness or loss of function
- ➢ Severe
  - ✓ Multiple and ulcerating lesion
  - ✓ Iritis, orchitis, nephritis or hepatitis
  - ✓ Nerve tenderness and loss of function

- ➢ **What is a relapse?**
  - ✓ Return of active disease after completion of prescribed treatment
  - ✓ When the BI at any site increases by at least 2+
  - ✓ Detection of active disease 2 years after completion of treatment
  - ✓ Relapse rate mono therapy era 20 -27%
  - ✓ Relapse with combination treatment 4-20%
  - ✓ Relapse after MDT less than 1% with the 2 years of MDT/ MB
  - ✓ Relapse after 1year MDT/MB not yet known
- ➢ **How to recognize relapse**
  - ✓ Active lesion
  - ✓ Increase in BI
  - ✓ New lesion
  - ✓ Erythema
  - ✓ Neuritis
  - ✓ Deterioration of nerve functions
- ➢ **Clinical features**
  - ✓ New lesions
  - ✓ Extension of existing lesions

- ✓ Change in morphology of lesions
- ✓ Increase in number of lesions
- ✓ Erythema of lesions
- ✓ Neuritis
- ✓ New nerve function loss
- ✓ Eye symptoms e.g iritis

- ➢ **Management of relapse**
  - ✓ *Distinguish misclassified cases and defaulter*
  - ✓ *Treat all relapses with full WHO/MDT regimen*

3.12.11 Anthrax (ቁርባ)

3.12.12 Rabies (የእብድ ውሻ በሽታ)

3.12.13 Filariasis, Lymphatic (Elephantiasis)/ዝሆኔ/

3.12.14 COVID -19

2nd edition in near future

Chapter 4; Poisoning, Drug Overdose, and Envenomation

Dr. Mulualem. G

4.1 _Poisoning and over dose(መመረዝ)

- ➢ Poisoning is an exposure to an amount of substance that is likely to produce untoward effects in an individual.
- ➢ Poisoning represents the harmful effects of accidental or intentional exposure to toxic amounts of any substance. The exposure can be by ingestion, inhalation, injection, or through skin.
- ➢ The effects may occur immediately or several hours or even days after the exposure.
- ➢ The damage could be local or systemic.
- ➢ Poisoning can be from
  - ✓ household substances (e.g. bleach),
  - ✓ industrial (e.g. methanol)
  - ✓ pesticides (e.g. organophosphates)
  - ✓ therapeutic medicine overdose (e.g. phenobarbitone, Amitriptyline)

- ✓ toxic plants (e.g. poisonous mushrooms, toxic herbal medications)
- ✓ bites and stings of venomous animals (e.g. snakes, bees).

Clinical features

- ➢ Clinical presentation is variable depending on the type of poison/medicine, route and dose.
- ➢ Many of the manifestation are nonspecific.
- ➢ Toxidromes are sets of clinical findings which could help in guiding the possible class of the poison/medicine
- ➢ It is very helpful to have a sample of the substance or the container in which it was stored as only few poisons can be identified instantly

Table; Toxidromes

Toxidrome	Mental status	Pupil	Vital signs	Other	Examples of toxic agents
Cholinergic	Confusion Coma	Miosis	Bradycardia Hypertension or Hypotension	Salivation, urinary & fecal incontinence, diarrhea, vomiting, lacrimation, bronchoconstrictio, fasciculations, weakness, seizures	Organophosphate and carbamate insecticides, nerve agents,
Anticholinergic	Agitation, hallucinations, delirium with mumbling speech, coma	Mydriasis	Hyperthermia, tachycardia, hypertension, tachypnea	Dry skin & mucous membranes, decreased bowel sounds, urinary retention, myoclonus, choreoathetosis	Antihistamines, tricyclic antidepressants, antiparkinson agents, antispasmodics, phenothiazines, atropine
Tricyclic antidepressant	Confusion, agitation, coma	Mydriasis	Hyperthermia, tachycardia, hypertension then hypotension	Seizures, myoclonus, choreoathetosis, cardiac arrhythmias	Amitriptyline, nortriptyline, imipramine,
Sedative- hypnotic	CNS depression, stupor, coma	Miosis	Hypothermia, bradycardia, hypotension, hypoventilation	Hyporeflexia	Benzodiazepines, barbiturates, alcohols,
Opioid	CNS depression, coma	Miosis	Hypothermia, bradycardia, hypotension, hypoventilation	Hyporeflexia pulmonary edema, needle marks	Opiates (eg, heroin, morphine, methadone, oxycodone)
Sympathomimetic	Hyperalert, agitation, hallucinations, paranoia	Mydriasis	Hyperthermia, tachycardia, hypertension, widened pulse pressure, tachypnea,	Diaphoresis, tremors, hyperreflexia, seizures	Cocaine, amphetamines, ephedrine, pseudoephedrine, phenylpropanolamine, theophylline, caffeine

Investigations

- ✓ RBS
- ✓ CBC

- ✓ U/A
- ✓ Electrolytes
- ✓ BUN and creatinine
- ✓ LFT
- ✓ Urine HCG → Routine urine pregnancy testing is strongly recommended in all women of childbearing age
- ✓ ECG
- ✓ CXR → for possible aspiration pneumonia
- ✓ Toxicological analysis of identified substance (e.g. Gastric aspirate) or from serum → if available

General Management for poisoning and overdose

Mgt principle (Supportive care)

Identify the substance

- — Obtaining the original toxic substance
- — Containers found near or on patient
- — Through accurate history

ABC of life

Left lateral positioning

Oxygen, monitors, IV access (determine RBS and draw sample for other investigation while securing IV line)

Treatment of seizures

Correction of temperature abnormalities and metabolic derangements

Drugs: Consider universal antidotes (Thiamine, Oxygen, Naloxone, Glucose)

Decontamination

Specific antidotes and other supportive care

Pharmacologic and other cares

- ☛ **Prevention of further poison absorption**
  - ○ Gastric lavage
  - ○ Decontamination of eye
  - ○ Skin decontamination
  - ○ Activated charcoal
- ☛ **Enhancement of elimination**
  - ○ Multiple-dose activated charcoal
  - ○ Haemodialysis
  - ○ Urinary pH alkalization
  - ○ Hyperbaric oxygenation
- ☛ **Administration of anti-dotes**
  - ○ Neutralization by antibodies
  - ○ Metabolic antagonism

  - Physiologic antagonism
- **Prevention of re-exposure**
  - Child-proofing
  - Psychiatric referral
- For Comatose pts…
  - Search for Hypoxia, Opioid intoxication, hypoglycaemia, and Wernicke's encephalopathy.
  - **Supplemental oxygen, Naloxone (for symptoms of opioid toxicity), 30ml of D50W and 100mg of thiamine known as the ‘coma cocktail’ can be administered**

Initial management

1. **Hypoglycemia**
   - **40% Dextrose**, IV, 40-60ml over 1-3 minutes *PLUS*
2. **Hypotension**
   - **NS**, 1000ml, IV fast then according to response
3. **Seizure management and medicine-associated agitated behavior**

   - **Diazepam 10mg**, IV, stat repeat doses as needed→ CAUTION-respiratory depression

- **Activated charcoal**
- **Catharsis**
  - Should be given only with the first dose of multiple dose charcoal in order to prevent electrolyte abnormalities and osmotic diuresis.
  - **Magnesium sulphate**, 250mg/kg or
  - **Sodium sulfate**, 250mg/kg
- **Alkalization of urine**

Decontamination

Skin decontamination

- Remove contaminated clothing and flush exposed areas with copious quantities of tepid (lukewarm) water or saline. Wash carefully behind ears, under nails, and in skin folds. Use soap and shampoo for oily substances.
- Always wear PPE to prevent secondary contamination to yourselves

Eye decontamination

- irrigate with copious amounts of water or saline for 10 — 15 minutes
- Ophthalmologic consultation is indicated for all ocular alkali injuries

GI Decontamination Principles

A. Activated charcoal
B. Ipecac syrup
C. Gastric (Orogastric) lavage
D. Whole bowel irrigation
E. Urine alkalinisation

A. Activated Charcoal

- **Activated charcoal**, 50 -100g (1- 1.5g/kg), P.O., or via NG tube, diluted in 400—800ml water stat
  - ✓ Activated charcoal may reduce systemic absorption of a variety of substances (especially from GIT).
  - ✓ The greatest benefit **(indication)** is achieved if activated charcoal is given **within 1 hour after ingestion.**
  - ✓ **Charcoal administration has become the decontamination strategy of choice to prevent poisoning after toxicant ingestion**
  - ✓ When mixing, add a small amount of water to charcoal in a container cap and shake container to make a slurry and then dilute further.
- ***Complication:*** no systemic effects, but may induce vomiting, constipation, diarrhoea, Bowel perforation or obstruction following multidose charcoal administration, aspiration of the activated charcoal and impaired absorption of orally administered antidotes.
- ***Avoid (no value):*** strong acids, alkali, corrosives, heavy metals, cyanides, lithium, hydrocarbons (paraffin), methanol and ethylene glycol.
- Contraindications:
  - ✓ Known or suspected GI perforation
  - ✓ GCS <8 (LOC) or declining rapidly (risk of aspiration)
  - ✓ unprotected airway.
  - ✓ Known ingestion of substance that charcoal does NOT adsorb.

Multiple Dose activated Charcoal

- *Dose:* **initial dose of 50 to 100 g (**1 -1.5g/kg**), PO or via NG tube, followed by 50g PO every 4hrs (in case of intolerance 25 g every 2 hours)** /0.5 - 1g/kg/, until clinical conditions and lab parameters improves
- Multiple doses can enhance elimination of drugs already absorbed into the body by interrupting enterohepatic circulation of drugs excreted into the bile.
- *Indication:* ingestion of large doses of Carbamazepine, dapsone, phenobarbitone, quinine, theophylline, Salicylates, sustained release formulations.
- ***Contraindications:*** diminished bowel sounds, proven ileus or small bowel obstruction.

B. Syrup of Ipecac → Induction of vomiting

Dose; Ipecac syrup (7%), 15-30ml, PO, stat

- ☛ May repeat once with 15ml if vomiting doesn't occur 20-30min
- ☛ If vomiting doesn't occur within 30-45min after second dose, perform gastric lavage
- ☛ Ipecac is no longer recommended for poisoning; Activated charcoal is treatment of choice

Indications

- ✓ Very recent ingestion (<1hr)
- ✓ Toxin known not to cause decreased LOC
- ✓ Toxin known not to fit through OG tube

Contraindications

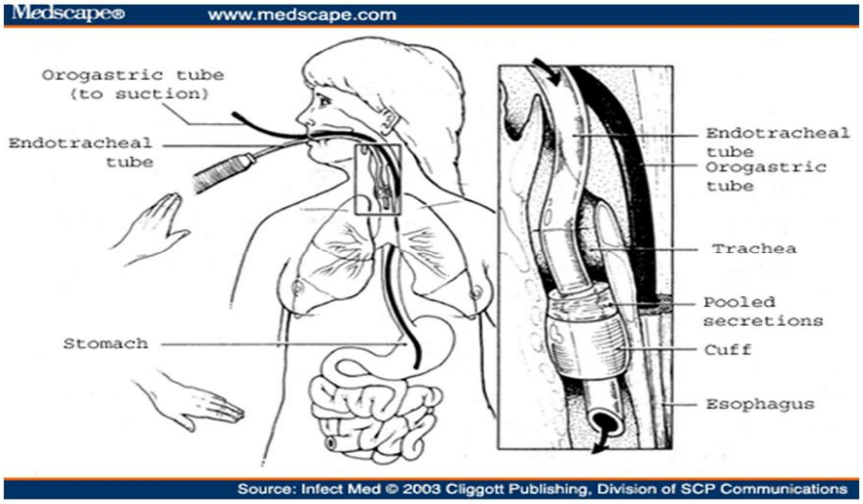
- ✓ Ingestion > 1 hr ago
- ✓ Toxin known to cause decreased **LOC/seizure**
- ✓ Caustics, hydrocarbons, TCAs

C. Gastric lavage (Orogastric Lavage)

- Indicated for ingestion of large amounts of tablets and capsules with a high inherent toxicity within 2 hrs.
- *procedure:*
  - ✓ *Place patient head* tilted 20 degrees downward *and* in left lateral decubitus position
  - ✓ Intubate patient, if they can't protect their airway
  - ✓ *Insert a large bore orogastric tube (32-40 F)*
  - ✓ *Aspirate fluid from stomach prior to fluid lavage*
  - ✓ ***Install warm tape water or saline** into stomach: **200-300ml (**10 **mL/kg in children)***
  - ✓ ***Aspirate fluid back & repeat till aspirate clears***
  - ✓ Consider administration of activated charcoal via orogastric tube before removal.

- ***Risks:*** pulmonary aspiration, epistaxis, laryngospasm, hypoxia, sinus bradycardia & mechanical injury
- ***Contraindications:***
  - ✓ patients with LOC
  - ✓ unprotected airway
  - ✓ ingestion of corrosives, volatile substances, hydrocarbons,
  - ✓ patients at risk of GI haemorrhage.

Gastric Lavage



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D. Whole Bowel Irrigation

- Instillation of large volumes of **laxative agent such as polyethylene glycol** in osmotically balanced electrolyte solutions
- Promotes rapid, mechanical elimination of ingested toxins
- **Not recommended for routine use** in the poisoned patient
- May be considered for substantial ingestions of iron, sustained release products, enteric coated products and symptomatic acute lead toxicity with known lead particles in the gastrointestinal tract. It has been used for other metal ingestions (e.g., lead), overdoses of sustained-release medications (e.g., lithium, theophylline), ingested pharmaceutical patches, and ingestions of vials or packages of illicit drugs.
- It might also be useful in particularly massive and/or late-presenting overdoses for which the efficacy of gastric emptying and/or charcoal is expected to be suboptimal.
- The technique may be used **by mouth in cooperative patients or by NG tube**;
- the usual recommended **dosing is 2 L /hour in adolescents and adults (500 mL /hour (25ml/kg/hr, maximum 2L/h) in children)**
- **Contraindication:** In ileus, bowel obstruction or perforation, and in patients with hemodynamic instability, Unprotected airway, hemorrhage, Intractable vomiting
- **Complications:** Nausea, vomiting, Pulmonary aspiration, Time consuming; possible delay instituting other definitive care

E. Urinary Alkalinisation

- Infusion of sodium bicarbonate to raise urinary pH to enhance clearance of toxins excreted by kidneys

- **Sodium bicarbonate** (NaHCO3), **IV,** 8.4%,
  - ✓ Bolus of 1-2ampules, IV, 50—100mEq (1-2 mEq/kg) in 1 L sodium chloride 0.45%. Administer 250—500mL over 1—2 hours.
  - ✓ Maintenance rate with 3 ampules of NaHCO3 in 1L of D5W at 1.5 X maintenance fluid rate for at least 4-6hrs
  - ✓ Target → continue treatment until
    - ☛ urinary pH 7.5-8.5 or
    - ☛ BP improves
  - ✓ Monitor electrolytes→ Pronounced hypokalemia may result from this technique. Thus, serum potassium must remain above 4 mEq/L to reliably achieve continuous urinary alkalinization.
  - ✓ Urinary pH should be monitored frequently (every 15 to 30 minutes) until the urine pH is 7.5 to 8.5.
  - ✓ Urinary alkalinization is sustained by either intermittent bolus or continuous infusion of bicarbonate.
  - ✓ Serum pH should not be allowed to rise above 7.5 to 7.55.
  - ✓ **This is a high-risk procedure and should only be performed in consultation with a specialist.** Risks associated with urinary alkalinization include volume overload (heart failure and pulmonary edema), pH shifts, and hypokalemia. Therefore, **contraindications to this procedure include patients who cannot tolerate the volume or sodium load, hypokalemic, or have renal insufficiency.**
  - ✓ **May be of benefit in salicylate, lithium, barbiturate and, TCA poisoning.**

- **Sodium bicarbonate** (NaHCO3)**,:** Oral:
  - ○ Initial: 48 mEq (4 g), then 12 to 24 mEq (1 to 2 g) every 4 hours
  - ○ dose should be titrated to desired urinary Ph
  - ○ maximum doses up to 16 g/day (200 mEq) in patients <60 years and 8 g (100 mEq) in patients >60 years.
  - ○ Administration of 48 mEq (4 g) every 8 hours for a total daily dose of 144 mEq (12 g) has also been shown to achieve a urinary pH of at least 7 after a period of 10 hours
  - ○ **Note:** Intravenous administration is preferred in specific overdoses (eg, salicylate) with a target urinary pH of 7.5 to 8.5

Universal Antidotes

- ➢ Thiamine
- ➢ Oxygen
- ➢ Naloxone
- ➢ Glucose

Table; Common antidotes

Poison	Antidote(s)	Dose for adults
Carbon monoxide	Oxygen	high-flow oxygen by tight-fitting facemask or ventilator
Benzodiazepines	Flumazenil	Initial dose: 0.1-0.2mg IV over 30-60 sec, repeat 0.1-0.2mg IV every minute up to 1mg
Acetaminophen	N-acetylcysteine	Initial oral dose: 140mg/kg, then 70mg/kg q 4h x 17 doses
Heparin	Protamine sulfate	1 mg neutralizes 90-115 U heparin; Initial dose: 1 mg/min to total dose 200mg in 2 h

Isoniazid	Pyridoxine (Vitamin B6)	Initial dose: 1 gm pyridoxine for every gm INH ingested or empiric 5gm IV over 10 min if amount ingested unknown
Opiates	Naloxone	Initial dose: 0.1-2.0mg IV push (opioid dependent patients should receive 0.1 mg IV every 30-60 sec until clinical response)
Ticyclic antidepressants	Sodium bicarbonate	Initial dose: 1-2 ampules (50-100mEq) IV push, then IV infusion to maintain blood pH 7.45-7.55 (Preparation: 3 amps 50mEq of NaHCO3 in 1liter D5W infused at 200-250 mL/h)
Organophosphates Carbamates Nerve agents	Atropine	Initial dose: 0.5-2.0mg IV; repeat q 3-5 min until sweat and secretions clear
	Pralidoxime	Initial dose: 1 gm IV over 15 min, then IV infusion of 3-4mg/kg/h for 24-72 hrs

4.2 Specific poisons

4.2.1 Organophosphates and Carbamates poisoning (ጸረ ተባይ፣ ተባይ ማጥፊያ፣ ማላታይን /በተለምዶ/)

- Organophosphates and carbamates also known as cholinesterase inhibitors are widely used as pesticides that may cause human poisonings after accidental or intentional exposure.
- Poisonings are particularly common in rural areas where more potent agents are widely available as agricultural insecticides and home use
- They can be absorbed via inhalation, ingestion, and skin contact.
- Examples:
    - ✓ Organophosphorus — **malathion, parathion**, TEPP, mevinphos (Phosdrin)
    - ✓ Carbamates- methiocarb, carbaryl, Sarin, soman, tabun.
- Patients present with muscarinic and nicotinic manifestations of intoxication.

Clinical features

- The killer signs are the 3B's:
    - ✓ Bradycardia
    - ✓ Bronchospasm
    - ✓ Bronchorrhea
- **Muscarinic overstimulation** causes
    - ✓ excessive salivation and sweating
        - ➢ severe diaphoresis can actually lead to dehydration with systemic hypovolemia
    - ✓ Lacrimation
    - ✓ Vomiting
    - ✓ Diarrhea
    - ✓ Bronchorrhea or bronchospasm.
    - ✓ abdominal cramping

Mnemonic for clinical features of Muscarinic overstimulation → DUMB BELL'S

- ✓ Diarrhoea
- ✓ Urination
- ✓ Miosis
- ✓ Bronchorrhea

- ✓ Bronchospasm
- ✓ Emesis (Vomiting)
- ✓ Lacrimation
- ✓ Low or high HR (brady/tachycardia)
- ✓ Salivation and sweating

- ✓ miosis
- ✓ bradycardia or tachycardia
- ☛ **Nicotinic overstimulation** causes
  - ✓ muscle fasciculations
  - ✓ Paresis or paralysis.
  - ✓ Death is usually caused by respiratory muscle paralysis.
  - ✓ Blood pressure and pulse rate may be increased because of nicotinic effects or decreased because of muscarinic effects.

Investigations

- ☛ Clinical
- ☛ Toxicological analysis

Treatment

- ☛ For all poisoning patients the principles of management are
  - ○ ABC's of life comes first→ Pay careful attention to respiratory muscle weakness; sudden respiratory arrest may occur.
  - ○ Give coma cocktail (Naloxone, thiamine, dextrose and oxygen),
  - ○ decontamination
  - ○ Antidote and
  - ○ Supportive care

Pharmacologic

- ➢ **Atropine**, 2 - 5 mg (0.05 to 0.1 mg/kg to children), IV, doubled every 5 min as needed to obtain and maintain full atropinization, which is indicated by an end point of clearing bronchial secretions and pulmonary rales.
  - ✓ Do not stop atropine therapy abruptly. Wean the rate of administration slowly.
  - ✓ During weaning monitor the patient for possible worsening.
  - ✓ Our goal in atropinazation is chest clearance and not tachycardia.
  - ✓ Therapy is continued until all absorbed organophosphate has been metabolized and may require 2 mg to more than 2g of atropine over the course of a few hours to several days. The most clinically important indication for continued atropine administration is persistent wheezing or bronchorrhea.
  - ✓ Note: Atropine will reverse muscarinic but not nicotinic effects.

Atropinisation

- 1 ampule (1mg/ml) = 1ml
- Start with 2mg
- Escalate every 5min by doubling the dose (i.e. 2mg →4mg → 8mg → 16mg)
- Maximum until chest is clear
- If the chest is clear give 20% of the last dose as follows
  - ✓ every 2hrs for 6hrs then
  - ✓ every 4hrs for 24 hrs then
  - ✓ QID → TID → BID →stop

- **Pralidoxime** (after atropinisation); 1- 2g (25 - 50 mg/kg, IV, administered in 100 mL of saline by infusion over approximately 30 minutes
  - ✓ In life-threatening situations, 50% of the initial pralidoxime dose may be infused over 2 minutes, followed by the remainder of the dose over 30 minutes.
  - ✓ After loading, a 1% concentration may be infused continuously at the rate of 500 mg/hr in adolescents and adults, or approximately 10 mg/kg/hr in children, and can be titrated to clinical effect.
  - ✓ Occasionally, **patients may require more than 48 hours of therapy; the end point should be persistent relief of neurologic and cholinergic signs.**
  - ✓ **After atropinisation** has been instituted, severe poisonings should be treated with the addition of pralidoxime.
  - ✓ This drug is **particularly useful** in poisonings characterized by **profound weakness and muscle twitching.**
  - ✓ **It is most effective if started within the first 24 hours of the exposure** before irreversible phosphorylation of the enzyme, but may still be effective if given late, particularly after exposure to highly lipid soluble compounds
  - ✓ **Pralidoxime (2-PAM, Protopam) is a specific antidote for organophosphate** toxicity, that acts to regenerate the enzyme activity at all affected sites (muscarinic, nicotinic, and probably CNS; however, it does not reactivate plasma cholinesterase).
  - ✓ Pralidoxime should be given immediately to reverse muscular weakness and fasciculations: •
  - ✓ **Pralidoxime is not generally recommended for carbamate intoxication**, because in such cases the cholinesterase inhibition is spontaneously reversible and short-lived. However, if the exact agent is not identified and the patient has significant toxicity, pralidoxime should be given empirically.
- **Note:** Organophosphates are usually dissolved in hydrocarbon bases; thus, prepare to treat hydrocarbon pneumonitis if it develops. Also, **bronchopneumonia that complicates the pulmonary edema has been observed in acute poisonings.**
- Because the organophosphates cause elevated levels of acetylcholine in the plasma, compounds that affect the uptake of acetylcholine and/or its release should be avoided in the management of these patients. Specifically, aminophylline and phenothiazines are

contraindicated.

- **Decontamination** → activated charcoal, gastric lavage… Do not induce vomiting because of the risk of abrupt onset of toxicity
- **Observe patients for at least 6—8 hours** to rule out delayed-onset symptoms resulting from skin absorption.

Order sheet example for organophosphate poisoning in our setup

- secure IV line
- keep NPO
- Irrigate the GI (Gastric lavage) *(if pt come to emergency within 1hr)*
- Put the pt in left lateral position
- Atropine 2mg, IV, Q5min, till atropinization (like after secretion stopped → lacrimation, urination, salivation…)
- Cimetidine, 400mg, IV, Loading followed by 200mg, IV, daily (if there is feature of GI irritation)
- Ceftriaxone 1g, IV, BID
- Metronidazole, 500mg, IV, TID

} if only there is aspiration pneumonia

4.2.2 Caustics Corrosives (በአሲድ ወይም ቤዝ መመረዝ

- Corrosives are chemicals primarily acids and alkali that cause tissue injury to a burn.
- **Acids** cause coagulation necrosis with eschar formation that limits penetration and depth of injury.
- **Alkali** cause liquefaction necrosis and penetrate more deeply. Alkali burns more common and worse than acid.
- Some corrosives can cause severe systemic toxicity and profound electrolyte disturbance.

Clinical features

- **After ingestion** of corrosive, hyper salivation, lethargy, polydipsia, vomiting, abdominal pain, dysphagia, pharyngeal edema, oral pain, drooling, and oral, esophageal, and/or gastric ulceration could occur.
- **Inhalation** of corrosive gases may cause upper respiratory tract injury, with strider, hoarseness, wheezing, and noncardiogenic pulmonary edema.
- **Eye or skin exposure** to corrosive causes instant pain and redness, followed by blistering. Conjunctivitis and lacrimation are common. Serious full-thickness burns and blindness can occur.
- **Significant injury:** airway compromise or gastrointestinal perforation complicated by peritonitis, mediastinitis, sepsis and shock.

Diagnosis

- Is based on history of exposure to a corrosive agent and Characteristic findings of skin, eye, or mucosal irritation and the presence of injury to the GIT.
- **Endoscopy:** indicated within 24 - 48 hrs of severe or deliberate ingestions. Endoscopy for all patients regardless of symptoms may be necessary.
- **CXR, and upright abdominal x-ray**; will show impacted button batteries, pneumomediastinum from esophageal perforation or free abdominal air from gastric perforation.
- **Other IX: RBS, CBC, electrolytes,** arterial blood gases,

Management

- **Inhalation:**
  - Give oxygen, and
  - follow closely for signs of airway obstruction or for non-cardiogenic pulmonary edema.
- **Chemical ingestion:**
  - Pre-hospital: immediately give water or milk to drink.
  - Gastric lavage & induction of vomiting are contraindicated.
  - Give activated charcoal if the ingested agent can cause significant systemic toxicity.
  - If there is esophageal perforation, avoid giving water as it may also enter to the mediastinum.
  - If esophageal or gastric perforation is suspected surgical consultation and repair immediately.
- **Chemical eye and skin burn:**
  - Remove all clothing, wash skin, and irrigate eyes with copious water or saline.
- **Button batteries:**
  - Immediately lodged endoscopy guided removal should be done immediately.
- **Antacids** are used for subsequent ulcer treatment
- use of steroids & antibiotics has no benefit.
- For most agents, there is no specific antidote.

4.2.3 Herbicides (ጸረ አረም፣ የአረም ማጥፊያ መርዝ) poisoning

- Herbicides are used as a weed killer which can cause human toxicity.

4.2.4 ChlorophenoxyHerbicides

- The most common agent in this group are
  - ✓ **2,4-dichlorophenoxyacetic acid (2,4-D)**→ locally available also as **Sura**
  - ✓ 2,4,5-trichlorophenoxyacetic acid (2,4,5-T);
  - ✓ 4-chloro-2 Methyl chlorophenoxyacetic acid;

- Human toxicity can occur after dermal contact, inhalation or ingestion.
- Muscle is the primary target

Clinical feature

- Eye and mucosal irritation after direct contact
- Nausea, vomiting and diarrhoea after ingestion
- Dyspnea, tachypnea and pulmonary edema after inhalational exposure
- Systemic toxicity (If large exposure) result in:
  - ✓ Neurologic toxicity (Mental status changes and seizures)
  - ✓ Cardiac toxicity (hypotension, tachycardia, and dysrhythmias);
  - ✓ Skeletal toxicity (muscle tenderness, fasciculation, rhabdomyolysis)

Diagnosis

- Made by exposure history, no specific tests for its detection;
- Baseline;
  - ✓ U/A → occult heme test positive in the presence of myoglobin)
  - ✓ ECG and monitoring
  - ✓ Creatinine phosphokinase (CPK)

Treatment

- Supportive → Decontamination measures
  - ✓ **Administer activated charcoal, then Perform gastric lavage**
  - ✓ **After lavage, give a dose of charcoal**
  - ✓ Skin decontamination if exposed
  - ✓ Urinary alkalinization is recommended for severely poisoned patients,
  - ✓ Hemodialysis can also be used
- **Respiratory support** for myopathic-related respiratory failure,
- No specific antidote
- Patients should be monitored for rhabdomyolysis and treated as necessary.
- **Asymptomatic or minimally symptomatic discharged after 4 to 6 hours of observation;**
- **Patients with muscle effects need Admission for Close observation and monitoring.**

4.2.4.1 Bipyridyl Herbicides (Paraquat and Diquat)

- Includes Paraquat and Diquat which are nonselective contact herbicides.

✓ Paraquat (1, 1-dimethyl-4, 4'-bipyridylium chloride)

- Available as a liquid concentrate (20%), as granules (2.5-10%), or an aerosol (0.2%)
- Fast-acting, nonselective herbicide, used for killing grass and weeds

- Plasma concentration peaks within minutes to 2 hours after ingestion, then distributed to most organs, with the highest concentrations found in the kidneys and lungs;
- In the lung paraquat accumulates and the high local oxygen tension generates a high levels of toxic oxygen species and subsequent damage
- In the kidney paraquat is concentrated during excretion, often leading to acute tubular necrosis, which may occur soon after ingestion (within 24 hours)
- Paraquat-induced renal dysfunction may decrease paraquat excretion, thereby enhancing overall toxicity
- A lethal oral dose of the 20% concentrate paraquat solution is about 10 to 20 mL in an adult and 4 to 5 mL in a child;
- Ingestion is responsible for the majority of paraquat deaths
- Inhalation exposure to sprays can be very irritating to conjunctiva and the airway but are unlikely to cause systemic toxicity

✓ Diquat

- Has similar structure, mechanism and lethal dose as paraquat
- Fewer occurrences of pulmonary injury and fibrosis because of diquat's lower affinity for pulmonary tissue
- Caustic to the skin and GI tract, and exposure can result in renal and liver necrosis.

Clinical feature **Bipyridyl poisoning (Paraquat)** → depend on route of exposure

- GI tract_ Ulceration of the lips, tongue, and pharynx within one to two days of ingestion, esophageal ulceration may proceed to esophageal perforation
- Skin –skin rashes (particularly on scrotal and intergluteal areas), cracked nails, and epistaxis
- Lungs – Inhalation may cause local toxic effects on bronchi, possibly resulting in cough, dyspnea, chest pain, pulmonary edema, epistaxis, and hemoptysis;
- Eyes –corneal exposure can cause ulceration and scarring
- Systemic toxicity
    - ✓ Multisystem effects include acute renal failure, cardiac failure, hepatic failure, and extensive pulmonary injury,
    - ✓ Evident within a few hours following large ingestions, but more typical manifestations of renal failure and hepatocellular necrosis develop between the second and fifth days, with progressive pulmonary fibrosis leading to refractory hypoxemia 5 days to several weeks later
    - ✓ Metabolic (lactic) acidosis is common as a result of pulmonary effects (hypoxemia) and multisystem failure;

Diagnosis

- Exposure history
- U/A
- Organ function test
- serum electrolyte
- CXR → may show pneumomediastinum/pneumothorax due to corrosive rupture of the esophagus

- Paraquat test in urine/ blood
- Serial pulmonary function test
- Arterial blood gas determinations
- Upper GI endoscopy if indicated

Treatment

- Admit any patient with Paraquat poisoning even if asymptomatic,
- Supportive care:
    - ✓ ABC of life
    - ✓ Antipain
    - ✓ Treatment of renal failure and complications
    - ✓ Treatment of infection,
- **Do not administer supplemental oxygen unless the patient is severely hypoxic**, because added oxygen stimulates superoxide radical formation and promotes oxidative stress
- Maintain intravascular volume and urine output to prevent pre-renal kidney injury,
- Decontamination
    - ✓ Remove clothing for splash
    - ✓ Skin washing with mild detergent for dermal contact
    - ✓ Irrigate eyes with saline/ copious water if conjunctivae exposure,
    - ✓ Lavage not routinely recommended unless patient present early and for ingested
    - ✓ Activated charcoal (1gm/kg up to 100 gm), and repeat dose in 1—2 hours
    - ✓ Prolonged Hemoperfusion or Hemodialysis two to three weeks, 4-6 hours daily,
- Repeated pulse doses of glucocorticoids and cyclophosphamide may improve survival in severe cases
- Treatment for diquat poisoning is similar to that for paraquat.

4.2.4.2 Organophosphate herbicides

- In addition to their use as insecticides, some organophosphate compounds are effective herbicides.
- Butiphos is used commonly as a cotton defoliant before mechanical harvesting.
- Treatment is identical to that for organophosphate insecticides.

4.2.5 Rodenticides (የአይጥ መርዝ እና የነቀዝ መድሃኒት)

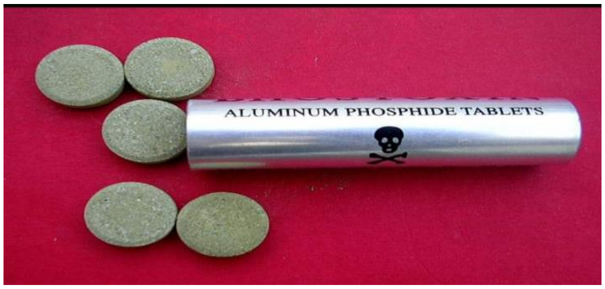
- Are chemicals used for extermination of rodents like rat and mouse; sometimes used as a grain preservative by destroying insects;
- Classified based on whether the agent has anticoagulant or non-anticoagulant effect,

A. Non-anticoagulant Rodenticides

- includes: **Zinc/ Aluminum Phosphide,** Arsenic, Barium carbonate/ hydroxide/ chloride/sulfide, Phosphorus (elemental/ yellow), sodium fluroacetate, Strychnine, Tetramine, Thallium Sulfate , ANTU, Bromethalin, Dicaboximide, Vacor.

Aluminum phosphide (የነቀዝ መድሃኒት) and Zinc Phosphide (የአይጥ መርዝ)

- Metal phosphides have been used as a means of killing rodents and are considered **single dose fast acting rodenticides** (death occurs commonly within 1 - 3 days after single bait ingestion).
- A bait consisting of food and a phosphide (usually zinc phosphide) is left where the rodents can eat it, are used to preserve grain, especially wheat, and to kill rats.
- Grain preservative is usually sold as tablets, and rat killer is sold as pellets.
- Examples of locally available poisons include: Celphos (Al Phosphide) 56%, Commando (Zn Phosphide) 80%, No Rat (Zn Phosphide).
- Cause Cellular toxicity and necrosis to the GI tract, kidney, and liver if ingested and to the lungs if inhaled;
- **Toxic dose**;
  - The LD50 zinc phosphide,
    - lowest reported lethal dose in humans is 4 g;
  - Aluminum phosphide
    - **Ingestion of as little as 500mg aluminum phosphide has caused death in an adult**
    - **It has high mortality rate (30 to 100%)**
    - **Survival is unlikely if > 1.5g is ingested.** *Since 1 tab is 3gram and patients have taken at least one tablet, mortality is 100% in our setup*



Picture; Aluminum phosphide tablets

Clinical feature

- The onset of symptoms is usually rapid, although delayed onset of pulmonary edema has been described;
- **If ingested;** Immediate nausea, vomiting, epigastric pain, phosphorous or fishy breath, black vomitus, and GI irritation or ulceration
- **Inhalation of** phosphine gas is associated with cough, dyspnea, headache, dizziness, and vomiting
- Myocardial toxicity, shock unresponsive to pressers, and acute lung injury, agitation, coma, seizures, hepato-renal injury, metabolic acidosis, hypocalcaemia tetany in both exposures has been observed;

Diagnosis

- Is based on a history of exposure to the agent
- IX; BUN & Cr, Electrolytes, liver transaminases, CXR, ABG or oximetry

Treatment

- **Emergency and Supportive care**
- **Decontamination** → Gastric lavage with potassium permanganate or combination coconut oil and 3- 5%sodium bicarbonate (Reduce stomach acid and resulting production of phosphine gas);
- **No specific antidote**
  - ✓ Magnesium sulphate IV with low dose of dopamine may be beneficial
  - ✓ Consider acetylcysteine
- Admit and observe for 48 - 72 hours for delayed onset of pulmonary edema,

B. Anti-coagulant rodenticides

- **First generation rodenticidal anticoagulants** →
  - ✓ They are less toxic than second generation agents.
  - ✓ E.g. Warfarin (Coumadin) is used therapeutically and as rodenticides;
- **Second generation agents**
  - ✓ They are far **more toxic than first generation**.
  - ✓ Lethal after a single ingestion of bait thus, they are sometimes referred to **as "super warfarin's"**
  - ✓ Examples of Super warfarin: Brodifacoum, Diphacinone, Bromadiolone, Chlorophacinone, Difenacoum, Pindone, and Valone;
  - ✓ Have profound and prolonged anticoagulant effects.
  - ✓ **Locally available brands include Zara.**
- Toxic dose: most warfarin-based rodenticides produce little effect after a single dose (10-20mg); While a single dose of super warfarin (as low as 1 mg) produce a significant clinical effect,

Clinical feature

- Seen as early as 8-12 hrs but mostly delayed by 1-2 days after ingestion and continue for days, weeks or months after super warfarin ingestion
- Sign and symptom of bleeding diathesis such as ecchymoses, subconjunctival hemorrhage, bleeding gums, or evidence of internal hemorrhage (eg, hematemesis, melena, or hematuria)
- the most immediately life-threatening complications are massive GI bleeding and ICH.

Diagnosis

- Based on exposure history
- Coagulation profile → Elevated levels of PT (INR) from admission level suggest poisoning and a normal PT level after 48 hrs of exposure rules out significant exposure
- CBC → Platelet count which may be used to rule out other causes of bleeding
- BG &RH and cross-match,

Treatment

- **Emergency and supportive treatment**
  - Treat hypervolemia/ shock with crystalloids,
  - Transfusion with whole blood or FFP
  - Consult neurosurgeon if intracranial bleeding suspected
  - Minimize or avoid invasive procedures like NGT insertion or endotracheal intubation if possible
  - Avoid drug, which may decrease metabolism of warfarin like cimetidine, sulfonamides, NSAID;
- **Antidote → Vitamin K** (phytonadione), effectively restores the production of clotting factors
  - 5-10mg very slowly IV/SC, max; 200 mg/d
  - Repeated may be required, especially in super warfarin product ingestion
  - Titrate Vit. K dose based on PTT level,
  - May require FFP/ whole blood transfusion for active bleeding as Vit. K take effect (6-24hr later).
- Decontamination: Activated charcoal can be used.
- Enhanced elimination has no role.

4.2.6 Ethanol (ከልክ ያለፈ ስካር፣ በአልኮል መመረዝ)

- Ethanol (CH_3CH_2OH) is the most common alcohol ingested as a recreation or used with other chemical or drugs intentionally as suicidal means.
- Its principal effects are GI irritation and intoxication; and it doesn't by itself produce metabolic acidosis.
- Toxicity most commonly occurs from ingestion, but ethanol may also be absorbed via inhalation or percutaneous exposure.
- A standard alcoholic beverage, such as 12 oz (355 mL) of **beer (2% to 6% ethanol by volume),** 5 oz (148 mL) of **wine (10% to 20%** ethanol by volume), or 1.5 oz (44 mL) of **80-proof spirits (40%** ethanol by volume), contains about 15 grams of ethanol.
- Ethanol may be found in high concentrations in many other common household products such as **mouthwash** (may contain up to **75%** ethanol by volume), **colognes and perfumes (up to 40% to 60%),** and as a diluent or solvent for medications (concentration varies widely between 0.4% and 65%), **hand sanitizers (Up to 60 -70%)**
- Some ethanol is broken down in the stomach by gastric **alcohol dehydrogenase**, which lowers the amount available for absorption by producing acetaldehyde. This enzyme is present at higher levels in men than in women, which may account for the fact that women usually develop a higher blood ethanol level than men after consuming the same dose per kilogram of body weight.
- Ethanol is a CNS depressant.

Clinical features

- The hallmark of ethanol toxicity is clinical inebriation.
- Behavioural disinhibition may initially appear as euphoria or agitation and combativeness.

- As intoxication becomes more severe, slurred speech, nystagmus, ataxia, and decreased motor coordination develop.
- Severe intoxication may cause respiratory depression and coma.
- Nausea and vomiting
- Peripheral vasodilation promoting hypothermia and flushed, warm skin may also lead to orthostatic hypotension (usually mild) and reflex tachycardia.
- Hypoglycaemia
- Lactic ketoacidosis.
- Alcohol withdrawal syndrome

Signs

- Look evidence of infections and traumatic injuries
- Depressed mental status

Diagnosis

- RBS
- serum alcohol levels in patients with altered mental status of unclear cause.

Treatment

- Management is observation until sobriety.
- Treat hypoglycaemia with IV glucose 0.5 to 1 grams/kg
- long-term drinkers are sometimes treated with IV fluids containing magnesium, folate, thiamine, and multivitamins, termed a *banana bag* because of the yellow color imparted by the multivitamin mixture.
- Wernicke's encephalopathy (characterized by abnormal mental status, ataxia, and nystagmus) requires daily treatment with thiamine, 100 mg, until normal diet is resumed.
- Prior to discharge, reassess for an underlying mental health disorder, such as suicidal or homicidal ideation, that requires further care or hospital admission.
- Clinical judgment, rather than a serum ethanol level, determines the appropriateness of discharge.
- Discharge the patient in the care of a responsible companion.

4.2.7 Household Products

4.2.7.1 Detergents (መንጽህ)

- Detergents are synthetic surface-active agents containing chemical products used at home.
- Most products contain bleaching (chlorine-releasing), bacteriostatic (having a low concentration of quaternary ammonium compound), or enzymatic agents.
- Detergents may cause skin irritation and have sensitizing properties.
- **Mortality and serious morbidity are rare.**

Clinical presentation

- Nausea, vomiting, and diarrhoea, hematemesis may occur and as a result secondary dehydration and electrolyte imbalance may develop.
- Mild ocular irritation is possible.
- Dermal contact generally causes a mild erythema or rash

Diagnosis:

- Based on history of exposure.
- IX; RBS, Electrolytes, glucose, calcium and Phosphate (after ingestion of phosphate-containing products, Methaemoglobin (Cationic detergents)

Treatment

- In patients with protracted vomiting or diarrhea, administer IV fluids to correct dehydration and electrolyte imbalance.
- If corrosive injury, use the management guideline for corrosive ingestion.
- If hypocalcaemia occurs after ingestion of a phosphate-containing product, give IV calcium.
- **Decontamination:**
    - ✓ dilute orally with small amounts of water or milk.
    - ✓ Do not induce vomiting because of the risk for corrosive injury.
    - ✓ Consider gastric lavage only for massive ingestions.
    - ✓ Activated charcoal is not effective.
    - ✓ In severe cases anti-emetics may be required (e.g., metoclopramide, 1omg /0.2—0.4 mg/kg/, PO, SC, or IM, QID based).
- **Eyes and skin exposure**→ irrigate with copious amounts of tepid water or saline. Consult an ophthalmologist if eye pain persists or if there is significant corneal injury.

4.2.7.2 Sodium Hypochlorite /Bleach/(በረኪና)

- **Sodium hypochlorite** is a chemical commonly found in bleach, water purifiers, and cleaning products.
- Sodium hypochlorite is a green/yellow liquid with the characteristic smell of chlorine and it is commonly known as bleach (berekina).
- Household bleach usually contains approximately 5 % sodium hypochlorite, although some may contain up to 10 %...
- Chlorine gas produces a corrosive effect on contact with moist tissues such as the eyes and upper respiratory tract.

Clinical presentation

- **HEENT:** exposure to the fumes can cause burning in the eyes, ears, and nose, pain in the mouth, and pain in the throat
- **RS;** chest tightness, coughing and difficulty of breathing. In more severe cases increased breathing rate, wheezing, swelling of the airways and respiratory failure may occur, the onset of which may take up to 36 h.
- **Skin:** irritation of the exposed area. Burns and blistering have been reported.
- **GIT**: abdominal pain, vomiting

- **CVS**: Rare cases of cardiovascular collapse and shock are presumed to consider secondary to severe local injury.
- **Nervous system:** Lethargy, delirium and coma can occur in patients with severe respiratory effects.

laboratory studies

- For ingestion → CBC, electrolytes, and chest and abdominal x-rays to look for mediastinal or intraabdominal air, which suggests perforation.
- For inhalation, arterial blood gases and pulse oximetry.

Treatment

- **Emergency and supportive measures**
  - **Inhalation of chlorine gas:**
    - ✓ **Immediately remove victim from exposure**
    - ✓ Give humidified supplemental **oxygen.**
    - ✓ **Observe** for **upper airway obstruction**, and intubate if necessary.
    - ✓ Use **bronchodilators for wheezing** and **treat non-cardiogenic pulmonary edema** if it occurs.

  - **Ingestion of hypochlorite solution:**
    - ✓ if a solution of 10% or greater has been ingested, or if there are any symptoms of corrosive injury (dysphagia, drooling, or pain), flexible endoscopy is recommended to evaluate for serious esophageal or gastric injury.
- **Decontamination**: for oral exposures, emesis and activated charcoal are contraindicated. Instead, immediately **give water by mouth**. Do not induce vomiting.
- **Skin and eyes**: remove contaminated clothing, and flush exposed skin immediately with copious water. Irrigate exposed eyes with water or saline. Bathing with mild shampoo and thorough rinsing for significant dermal exposures is recommended.

4.2.7.3 Dettol (ዲቶል)

- **Dettol** is a commonly available household disinfectant. It contains Isopropyl alcohol (12%), Chlorxylenol (4.8%), and Pine oil (9%).

Clinical presentation:

- It causes CNS depression, corrosion of oral mucosa and gastrointestinal tract (upper GI hemorrhage), laryngeal edema, upper airway obstruction, bronchospasm, nephrotoxicity, hepatitis and cardiac arrhythmias.
- The main risk of poisoning is aspiration with subsequent development of acute respiratory distress syndrome (ARDS), pneumonia and sudden cardio-respiratory arrest.
- Micro-aspiration has been hypothesized to be the reason for delayed upper airway obstruction that may occur in totally asymptomatic patients up to 48 h after admission.

Treatment:

- **The mainstay of dettol poisoning is supportive management along with close observation in hospital for stridor.**
- Emesis and gastric lavage should not normally be attempted. The only indication for gastric lavage in the acute setting is a patient who has consumed other poison along with Dettol.
- Patient should be started on IV fluids with regular monitoring of electrolytes.
- Adolescents and adults who have consumed more than 200 to 300 ml and children who have consumed lesser amounts should be kept NPO and watched carefully for signs and symptoms of nephrotoxicity and CNS depression.
- In case of severe poisoning or any evidence of hematuria or azotemia, do forced alkaline diuresis
- Exchange transfusion, and early dialysis for isopropyl alcohol can be attempted in rare patients who are deteriorating steadily despite adequate supportive measures.
- Even patients who arrive comatose to the ED frequently demonstrate a rapid and complete recovery. It is, however, important to monitor closely in hospital for strider for a minimum of 48 hours after admission.

4.2.8 Hydrocarbon (ጋዝ፧ቤንዚን፧ኪሮሲን) poisoning

- Hydrocarbons, or petroleum distillates, are widely used in the petroleum, plastic, agricultural, and chemical industries as solvents, degreasers, fuels, and pesticides.
- Examples—kerosene, turpentine substitutes, petrolatum, and benzene.
- Toxicity Caused by direct injury from pulmonary aspiration or systemic intoxication after ingestion, inhalation, or skin absorption.
- Aspiration leads to a necrotizing, potentially fatal chemical pneumonitis.
- CNS toxicity is manifested as alterations in mental status, including narcosis, inebriation, and frank coma.
- In addition to these toxicities, the solvents possess additional toxicities, including the risk of bone marrow injury (in the case of benzene → long term risk factor for hematologic malignancy).
- Aliphatic hydrocarbons and simple petroleum distillates such as lighter fluid, kerosene, furniture polish, and gasoline are poorly absorbed from the gastrointestinal tract and do not pose a significant risk of systemic toxicity after ingestion, as long as they are not aspirated. In contrast, many aromatic and halogenated hydrocarbons, alcohols, ethers, ketones, and other substituted or complex hydrocarbons are capable of causing serious systemic toxicity, such as coma, seizures, and cardiac arrhythmias.
- Inhalation of any hydrocarbon vapors in an enclosed space may cause intoxication as a result of systemic absorption or by displacing oxygen from the atmosphere.
- Dermal absorption can be significant for some agents but is insignificant for most of the simple, aliphatic compounds.

Clinical Presentation:

- Pulmonary presents as coughing, gagging, or choking. This may progress within a few hours' to tachypnea, wheezing, and severe chemical pneumonitis.
- Death may ensue from secondary bacterial infection and other respiratory complications.
- Ingestion often causes abrupt nausea and vomiting, occasionally with hemorrhagic gastroenteritis.
- Some compounds may be absorbed and produce systemic toxicity which includes confusion, ataxia, lethargy, and headache.
- With significant exposure, syncope, coma, and respiratory arrest may occur.

- Cardiac arrhythmias may occur owing to myocardial sensitization (with chlorinated and fluorinated compounds

Diagnosis: →based on history of exposure and typical findings.

Aspiration pneumonitis:

- ✓ If symptoms are not present within 6 h of exposure, it is very unlikely that chemical pneumonitis will occur.
- ✓ Chest x-ray and arterial blood gases or oximetry may assist in the diagnosis.

Systemic intoxication:

- ✓ diagnosis is based on history of ingestion or inhalation, accompanied by the appropriate systemic clinical manifestations.

Other useful laboratory studies:

- ✓ RBS
- ✓ electrolytes BUN, creatinine, liver transaminases
- ✓ chest x-ray
  - ➢ If the patient has any respiratory symptoms upon arrival to the ED, CXR should be obtained immediately. Symptoms occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 h, peaking in 48-72 h. **aspiration pneumonia features**, **Pneumatoceles and pleural effusions** may occur.
- ✓ ECG monitoring for suspected significant inhalation or ingestion.
  - ➢ Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid-base or electrolyte disturbances.
- ✓ ABG

Treatment

- Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support as necessary.
- Because most hydrocarbons cause clinical toxicity only when aspirated, the mainstay of treatment is to **leave ingested compounds in the gut (when possible) and to prevent emesis or reflux**.
- Gastric emptying is generally reserved only for those compounds with the potential for systemic toxic effects. Gastric emptying is always contraindicated in other cases.
- The mnemonic CHAMP refers collectively to the following hydrocarbons:

Camphor
Halogenated carbons,
Aromatic hydrocarbons
Metals and
Pesticides.

Patients who ingest these compounds in volumes >30 mL, such as might occur with intentional overdose, may benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration.

- Antibiotics should not be used prophylactically but should be reserved for specific infections if they develop.
- The use of **corticosteroids** in the treatment of aspiration is **not recommended**.
- In the event of hypotension or bronchospasm, epinephrine and other catecholamine containing **vasopressors**, (Dopamine and Norepinephrine) **are contraindicated** because hydrocarbons are known to cause ventricular irritability and predispose to fibrillation, an effect that is exacerbated by catecholamines.
- **Decontamination**
  - ✓ **Inhalation:** move the victim to fresh air and administer oxygen if available.
  - ✓ **Skin and eyes:** remove contaminated clothing and wash exposed skin with water and soap. Irrigate exposed eyes with copious tepid water or saline and perform fluorescein examination for corneal injury.
  - ✓ **Ingestion:** for agents with no known systemic toxicity, gut decontamination is neither necessary nor desirable because any gut-emptying procedure may increase the risk of aspiration.

4.2.9 Carbon monoxide poisoning (በጭስ መመረዝ)

- CO is an odourless, tasteless, colourless, non-irritating gas formed by Hydrocarbon combustion.
- Smoke inhalation is responsible for most inadvertent cases of CO Poisonings.
- CO binds to Haemoglobin with much higher affinity than oxygen (240 X) forms carboxyhaemoglobin & tissue oxygenation is impaired.

Clinical features

- Poisoning with carbon monoxide is common where there is incomplete combustion of charcoal.
- Patients may manifest symptoms ranging from mild confusion to coma.
- Acute poisoning results in headache, nausea and vomiting, mental confusion and agitation.
- Severe toxicity causes confusion, impaired thinking, and may progress to coma, convulsions, and death.

Investigations

- Clinical: Dx is based on a compatible **Hx and physical exam** in addition with an **elevated carboxyhaemoglobin** level measure by co oximetry of a blood gas sample.
- Toxicological analysis

Treatment

Non pharmacologic

- Supportive treatment
- Take the patient out to open air.

Pharmacologic

- The most important interventions in the management are removal from the CO source & administer **100% oxygen by face mask**
- Comatose patients should be intubated & mechanically ventilated using 100% oxygen.
- Hyperbaric oxygen

4.3 Snake bite (የእባብ ንክሻ)

- The majority of snakebites are non—poisonous; only few species are venomous (poisonous).
- Most common venomous snakes are the pit vipers (vasculotoxic) and the elapidae and hydrphidae (primarily neurotoxic).
- Children, because of their smaller body size, are far more likely to have severe envenomation.

Clinical features

Local signs and symptoms

- There will be an immediate **pain.**
- **Local bruises and persistent bleeding** from fang puncture.
- **Swelling** begins within 10-20 minutes. It may become extensive after viper and spitting cobras, involving whole limb or adjacent trunk or whole body in children.
- Draining **lymph nodes may become enlarged, painful and tender** within 30-60 minutes.

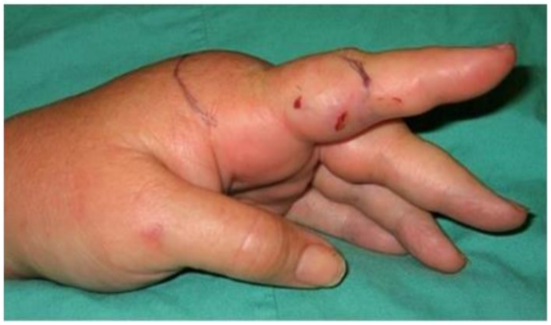


Figure: Moderately severe envenomation. Note edema and early ecchymosis 2 h after a bite to the finger

- **Blisters**, may appear near the fang marks in 12-24 hours.
- Demarcated pigmentation or depigmentation with anesthesia and a distinctive smell of putrefaction are sign of necrosis. This progresses to **frank necrosis with sloughing of dead tissue.**
- Increasing **myalgia**, blisters advances **to tissue necrosis and gangrene** will develope.

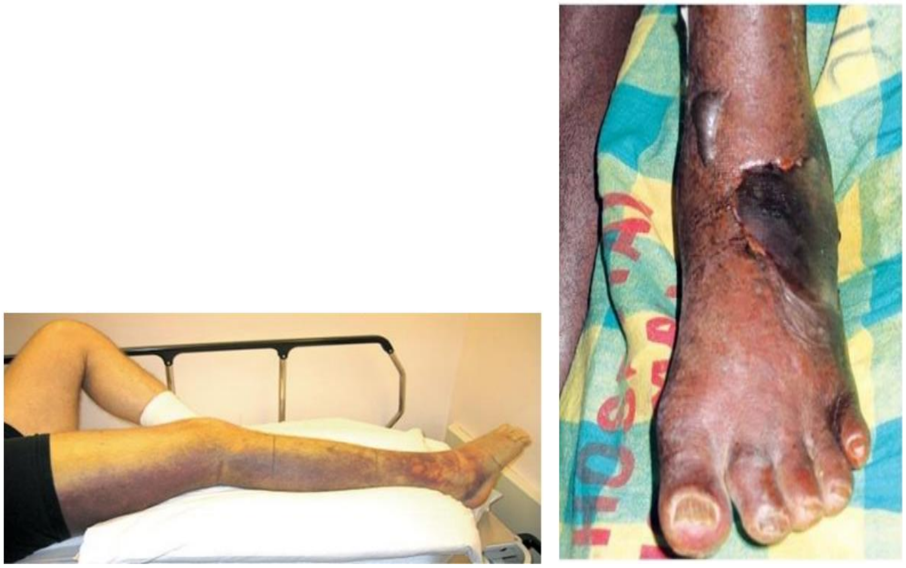
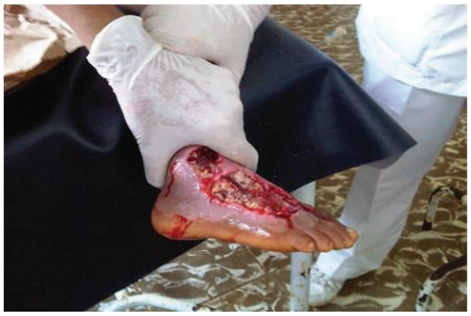


Figure: left) Severe envenomation. Note extensive ecchymosis 5 days after a bite to the ankle. Right) Early stages of severe, full-thickness necrosis 5 days after a viper bite



Figure; Severe necrosis 10 days after a pit viper bite in a young child

Systemic signs and symptoms

- Bleeding and clotting disorder:
    - There is local bleeding from wound, fang puncture and venepuncture site and systemic bleeding from coagulation abnormality and impaired platelets.
    - Spontaneous systemic bleeding (e.gs from gum and nose, hematemesis, rectal bleeding, hemoptysis, hematuria, retroperitoneal, intracranial bleeding and in pregnant woman ante-partum hemorrhage).
- Shock (hypotension): could be anaphylaxis or bleeding related or cardiotoxic effect.
- Progressive descending paralysis starting with dropping eyelids (ptosis) and pupillary abnormality, paralysis of eye movement causing diplopia(ophthalmoplegia),; paralysis of facial muscle, jaw, tongue, neck flexors causing “broken neck” sign, and other cranial palsies, difficulty of producing speech(dysphonia), difficulty of handling secretions(drooling) finally respiratory muscle and total flaccid paralysis.
- Acute renal failure may ensue because of hypotension or rhabdomyolysis.

severity of envenomation:

- **None ("dry bite"):** fang marks only
- **Mild:** local findings only. e.g., pain, local ecchymosis, non-progressive swelling
- **Moderate:** swelling (clearly progressing, systemic signs or symptoms, and/or laboratory abnormalities
- **Severe:** Respiratory distress, Neurologic dysfunction, and/or Cardiovascular instability/shock

Investigations

- CBC
- BG & RH
- urinalysis for presence myoglobin or blood
- BUN and Creatinine
- LFT
- PT/INR/PTT
- Electrolytes
- Whole blood clotting test (leave 2-5ml of blood in dried test tube. Failure to clot after 20 minutes implies in coagulable blood)

N.B. Avoid venepuncture in state of generalized bleeding

Treatment

Non pharmacologic

First Aid

- A significant proportion of snake bites do not result in envenomation……observe if no clinical features of local/systemic sign and/ or symptoms;
- Move patient to a safe area

- Remove anything tight around the bitten area (ankle bracelets, Rings)
- Splint the limb below the level of the heart to reduce movement and absorption of venom if the limb is the affected organ; apply a firm bandage to affected limb from fingers or toes to proximal site of bite.
- Do not move the limb
    - Carry the person on a stretcher and tie the limb to a straight piece of wood.
    - C lean the wound and reassure the patient.

At the hospital

- Bed rest, reassure, keep warm
- Assess patient's airway, breathing and circulation (ABC of resuscitation)
    - Give NS infusion (bolus of 20—40 mL/kg) if the patient is hypotensive; if hypotension persists, consider anti-venom. Only after aggressive volume resuscitation and antivenom administration; if the shock unresponsive, vasopressors (e.g., adrenaline, dopamine) should be added.
    - With any evidence of difficulty swallowing or breathing, proceed with endotracheal intubation and ventilatory support (may be required for days or weeks).
    - Paralysis of respiratory muscles can last for days and requires intubation and mechanical ventilation or manual ventilation;
- For probable venomous bites:
    - Measures applied in the field (such as constriction bands) should be removed once IV access has been obtained
    - Clean site of bite with antiseptic lotion or soap and water
    - Do not attempt to suck or make any incisions at the site of the bite
    - Leave wound open; punctured wounds are especially likely to be infected.
    - Avoid intramuscular injections
    - In acute renal failure dialysis (peritoneal or hemodialysis), usually reversible
    - If the snake is identified as non-poisonous or there is absence of swelling or systemic signs after 6 hours reassure the patient
    - Surgical debridement when required

Pharmacologic

- If any evidence of **neurologic dysfunction** (e.g., any cranial nerve abnormalities such as ptosis or inability to maintain upward gaze):
    - Pre-treat with **atropine**: 0.6 mg IV (children, 0.02 mg/kg; min. of 0.1 mg) **Followed by a trial of anticholinesterase inhibitors**
        - **Neostigmine**: 1.5—2.0 mg IM (children, 0.025—0.08 mg/kg)
        - If objective improvement is evident at 5 min, continue neostigmine at a dose of 0.5 mg (children, 0.01 mg/kg) IV or SC every 30 min as needed, with continued administration of atropine by continuous infusion of 0.6 mg over 8 h (children, 0.02 mg/kg over 8 h).
- Prophylactic antibiotics are unnecessary unless prehospital care included incisions or mouth suction.

- **If there is secondary infection**:
  First line
  - **Amoxicillin/clavulanic acid,** 500/125mg, (i.e. Augmentin, 625mg), PO, TID for 5-7 days.
  - **Immunization, primary or booster**:
  - **Tetanus toxoid vaccine**, IM, 0.5mL immediately.
- **Analgesia**
  For mild pain:
  - **Paracetamol**, 1g, P.O, 4-6 hourly when required to a maximum of 4 doses per 24 hours.

  For severe pain: ADD
  - ☛ **Tramadol**, 50-100mg, 2-3X per day

N.B. The use of an NSAID is not recommended due to the potential danger of AKI in a hypotensive patient.

Polyvalent antivenom

Indications for polyvalent antivenom:

- worsening of local injury (e.g., pain, ecchymosis, or swelling)
- Abnormal results on laboratory tests (e.g., worsening platelet count, prolonged coagulation times)
- Systemic manifestations (e.g., unstable vital signs or abnormal mental status).
- All patients with confirmed mamba bites before symptom onset
- Patients with confirmed puff adder or Gaboon adder bites should receive antivenom at the onset of any symptoms

N.B.

- ☛ In most cases patients do not need and should not be given antivenom.
- ☛ The dose of antivenom is the same for adults and children.
- ☛ Serum sickness is a relatively common adverse event.
- ☛ Even after the administration of antivenom, patients with neurotoxic snakebites may need ventilation.

Polyvalent snake antivenom

- slow IV infusion. **Dilute 100 mL in 300ml of NS.** Administer **slowly for the first 15 minutes**, as most allergic reactions will occur within this period. Increase the flow rate gradually to **complete the infusion within one hour.**
  - Prepare IM epinephrine (adrenaline) and IV chlorpheniramine, be ready if allergic reaction occurs when antivenum given.
  - Before giving the anti-venom, perform skin test with 0.02 to 0.03 ml in 1:10 dilution, subcutaneous, to test for anaphylaxis. If itching/urticarial rash, restlessness, fever,

cough or difficult breathing develop, then stop anti-venom and give epinephrine (adrenaline).

- **Start giving the antivenom with minimal dose for mild cases with a minimal dose of 22-40 ml and give a maximum of 200-400 ml. Blood transfusion should not be required if anti-venom is given.**
- Continue to observe for progression of edema and systemic signs of envenomation during and after antivenom infusion.
  - ✓ Measure limb circumference at several sites above and below the bite
  - ✓ outline the advancing border of edema with a pen every 30 minutes.
  - ✓ These measures serve as an index of the progression as well as a guide for antivenom administration.
- More anti-venom should be given after 1—2 hr if the patient is continuing to bleed briskly or has deteriorating neurotoxic or cardiovascular signs.
- Repeat laboratory determinations every 4 hours or after each course of antivenom therapy, whichever is more frequent. Repeat if there is no clinical improvement after the infusion.
- Clotting function returns to normal only after clotting factors are produced by the liver.
- Response of abnormal neurological signs to anti-venom is more variable and depends on type of venom
- Neurotoxicity from elapid bites (cobra and mamba) may be harder to reverse with antivenom. Once neurotoxicity is established and endotracheal intubation is required, further doses of antivenom are unlikely to be beneficial. In such cases, the victim must be maintained on mechanical ventilation until recovery, which may take days or weeks.
- Mild hypersensitivity reactions should not be a reason not to give polyvalent.
- If acute reaction to antivenom develops and depending on severity of reaction:
  - Stop infusion.
  - Treat with standard doses of epinephrine (IM or IV; IV route only in the setting of severe hypotension)
  - Antihistamines (IV) e.g., Diphenhydramine, 1 mg/kg to a max. 100 mg, plus Cimetidine, 5—10 mg/kg to a maximum of 300 mg
  - IV glucocorticoids
  - When reaction is controlled, restart antivenom ASAP if still indicated (may further dilute in a larger volume of NS).

Surgical Management

- Seek surgical opinion if there is severe swelling in a limb, it is pulseless or painful or there is local necrosis
- Surgical care will include:
  - Intact serum-filled vesicles or hemorrhagic blebs should be left undisturbed. If ruptured, they should be debrided with sterile technique.
  - Excision of dead tissue from wound
  - Incision of fascial membranes to relieve pressure in limb compartments, if necessary

  - Skin grafting, if extensive necrosis
- Antibiotic treatment is not required unless there is tissue necrosis at wound site
- Tracheostomy (or endotracheal intubation) if paralysis of muscles involved in swallowing occurs
- Bite in the hand, fore-arm or leg may be complicated by muscle-compartment syndrome If there are signs of **compartment syndrome**
  - ✓ **elevate the leg**
  - ✓ consider **additional dosing** of the infusion
  - ✓ consider **fasciotomy** if there is no response for conservative management.

Monitoring

- Monitor very closely immediately after admission, then hourly for at least 24 hours as envenomination can develop.
- Any patient with signs of envenomation should be observed in the hospital for at least 24 h, Patients whose condition is not stable should be admitted to an intensive care setting
- Measure/record circumferences of the bitten extremity every 15 min until swelling has stabilized; while monitoring, the extremity should be positioned at approximately heart level.
- Admit to hospital. (If no evidence of envenomation, monitor for 8 h before discharge.)
- Institute monitoring (cardiac and pulse oximetry)
- Vital signs, cardiac rhythm, oxygen saturation, urine output.
- At discharge, victims of venomous snakebite should be warned about possible recurrent coagulopathy, signs and symptoms of wound infection, antivenom-related serum sickness

4.4 Specific Drug Overdoses (እጅግ ከመጠን በላይ የሆነ መድሃኒት በመውሰድ መመረዝ)

4.4.1 Acetaminophen/Paracetamol/ overdose

- ✓ Acetaminophen or Paracetamol having many brand names is a widely used drug found in many over the counter and prescription analgesics and cold remedies.
- ✓ **Paracetamol overdose can cause Hepatotoxicity, Renal damage, Fetal death** and **spontaneous abortion:**
- ✓ **Toxic dose**; **Acute ingestion** of > 6—7 g (>150—200 mg/kg in children) or in adults' is potentially hepatotoxic.
- ✓ **Chronic toxicity** may happen after daily consumption of high therapeutic doses (4—6 g/day) for 24hr or more by alcoholic patients. Children have developed toxicity after receiving as little as 60— 150 mg/kg/day for 2—8 days.
- ✓ **High-risk patients for toxicity** include; If the patient is alcoholic, malnourished, or fasting, or taking drugs that induce P-450 activity (e.g., anticonvulsants, INH)

Clinical Presentation

- ✓ Clinical manifestations depend on the time after ingestion.
- ✓ **Early:**
  - usually no symptoms other than anorexia, nausea, or vomiting. Rarely, a massive overdose may cause altered mental status and metabolic acidosis.
- ✓ **After 24—48 hrs**
  - when AST and ALT level rise, hepatic necrosis becomes evident.
  - If **acute fulminant hepatic failure** occurs, encephalopathy and death may ensue.
  - Encephalopathy, metabolic acidosis, hypoglycaemia, and progressive rise in the prothrombin time are indications of severe liver injury and has poor prognosis.
  - **Acute renal failure** occasionally occurs, with or without concomitant liver failure.

Investigation

- ✓ **RBS**
- ✓ **Electrolytes**
- ✓ **BUN and creatinine** → the renal injury manifested after 2-3 days
- ✓ **liver enzymes**
- ✓ **PT, INR**
- ✓ **Urine HCG**→ because acetaminophen cross placenta by 14 weeks. So, antidote should be considered in pregnancy ASAP.
- ✓ ECG → to exclude the presence of co-ingested cardiotoxic substances.
- ✓ Abdominal U/S → may reveal hepatic enlargement, renal abnormality, and inflammatory changes.
- ✓ CT→ to see cerebral edema and encephalopathy in For patients with altered mental status
- ✓ Interpretation of serum acetaminophen level lab result is based on Rumack-Matthew nomogram *(refer Poisoning and Drug Overdose Management Training for Health Care Professionals, FMOH, Ethiopia, 2020)*

Treatment

A. Emergency and supportive measures:

- ✓ antiemetic (metoclopramide or ondansetron) for Spontaneous vomiting
- ✓ Provide general supportive care for hepatic or renal failure if it occurs.
- ✓ Treatment for acetaminophen-induced fulminant hepatic failure includes acetylcysteine therapy, correction of coagulopathy and acidosis, monitoring for and aggressive treatment of cerebral edema, and early patient referral to a liver specialty/transplant centre if available.

B. Decontamination:

- ✓ **Prehospital.** →
  - activated charcoal, if available.

- Ipecac-induced vomiting may be useful for initial treatment of children at home if it can be given within 30 min of exposure.
- ✓ **Hospital.**
- activated charcoal. **It should be given before po NAC. This is because activated charcoal will adsorb the po NAC**
- Gastric emptying is not necessary if charcoal can be given promptly.

C. Specific drugs and antidotes:

NAC (N-Acetylcysteine)

- ✓ **Indication** to Consider giving NAC
- if the patient is at increased risk for toxicity (if patient falls within a high-risk group)
- multiple or subacute overdoses
- time of ingestion is uncertain or unreliable.
- In chronic acetaminophen ingestions, NAC treatment is advised
- ➢ if the amount ingested was more than 150—200 mg/kg or 6—7 g within a 24-hour period
- ➢ if liver enzymes are elevated
- ✓ **NAC ORAL**; loading dose of 140 mg/kg PO, followed by 70 mg/kg every 4 h for 17 more doses over 72 h (a total of 18 doses).
- If stat serum levels of acetaminophen are not immediately available, initiate antidote therapy with NAC
- Maximal benefit, if it is started within 8— 10 h and of diminishing value after12—16 h. However, treatment should not be withheld, even if the client comes as late as 48 h post ingestion
- If the patient vomits, repeat the dose.
- If vomiting interferes with oral acetylcysteine administration, give it by gastric tube and use antiemetic or give the NAC iv if necessary.
- ✓ **IV NAC;**
- It is recommended if there is altered mental status or severe vomiting. However, mostly oral NAC has bad odour and unpleasant test.
- **Continuous IV infusion** is recommended for **acute ingestion**, as follows:
- ➢ **Loading dose:** 150 mg/kg IV; mix in 200 mL of D5W and infuse over 1 hr.
- ➢ **Dose 2:** 50 mg/kg IV in 500 mL D5W over 4 hrs
- ➢ **Dose 3:** 100 mg/kg IV in 1000 mL D5W over 16 hrs.
- **Intermittent iv infusion** may be considered for **late-presenting or chronic ingestion**.
- ➢ A loading dose of 140 mg/kg iv (diluted in 500 mL D5W), infused over 1 hr.
- ➢ Maintenance doses of 70 mg/kg IV, given every 4 hours for at least 12 doses (dilute each dose in 250 mL of D5W and infuse over a minimum of 1 hr.)
- The duration of IV NAC is for only 20 hrs.
- ✓ Once the standard treatment duration has elapsed, only **discontinue** therapy **if the serum acetaminophen level is below the limits of detection, liver transaminase levels are normal, and the patient is asymptomatic**. If there is evidence of hepatic toxicity, then NAC should be continued until this has resolved.
- ✓ **Treatment may be stopped 36 h after the last dose of acetaminophen if the liver enzymes are normal.**

- All patients requiring acetylcysteine therapy should be admitted to the hospital until the completion of the therapy. In general, admission to a hospital bed is adequate unless the co-ingestant is of concern, hepatotoxicity is severe, or the patient is suicidal, and 24-hour direct observation cannot be arranged.
- Patients who are not at risk for developing acetaminophen-induced hepatotoxicity (e.g., acetaminophen concentration below the nomogram or unmeasurable acetaminophen concentration with normal hepatic transaminase concentrations) should be observed in the ED for 4-6 hours to exclude potentially toxic coingestants before disposition.

4.4.2 NSAIDs Overdose

- NSAIDs and are widely used for control of pain and inflammation.
- Overdose by most NSAID usually produces **only mild GI upset.**
- CNS, hemodynamic, pulmonary, and hepatic dysfunction also occur with some NSAD's.
- **Significant symptoms occur after ingestion of more than 5-10 times the usual therapeutic dose.**

Clinical presentation

- Generally, Asymptomatic or have mild GI upset (nausea, vomiting, abdominal pain, and sometimes hematemesis).
- Occasionally, patients exhibit drowsiness, lethargy, ataxia, nystagmus, tinnitus, and disorientation.
- With the more toxic agents and with massive ibuprofen overdose, seizure, coma, renal failure, and cardiorespiratory arrest may occur.
- Rarely Hepatic dysfunction, hypoprothrombinaemia, and metabolic acidosis.

Investigation

- RBS
- U/A
- CBC
- Electrolytes
- BUN & creatinine
- liver transaminases
- PT, aPTT

Treatment

- ✓ ***Emergency and supportive measures:***
  - Maintain an open airway and assist ventilation if necessary
  - Administer supplemental oxygen.
  - Treat seizure, coma, and hypotension if they occur
  - Antacids may be used for mild GI upset.
  - Replace fluid losses with IV crystalloid solutions.
- ✓ ***Decontamination:***
  - **Prehospital:** consider activated charcoal if available and the patient is alert
  - **Hospital:** consider **activated charcoal**. Gastric emptying is not necessary for most ingestion if activated charcoal can be given promptly. Consider **gastric lavage** for massive overdoses
- ✓ **There is no antidote.** Vitamin K may be used for patients with elevated PT caused by hypoprothrombinaemia.

4.4.3 Cardiac glycosides (digoxin and digitoxin) overdose

- ✓ Cardiac glycosides are used therapeutically as **digoxin and digitoxin**.
- ✓ **Toxic dose;** Healthy adults may develop symptoms after ingestions of more than 2-3 mg of digoxin but rarely develop severe toxicity with ingestions less than 5mg.Toxic effects in children are likely with ingestions of more than 0.1mg/kg of digoxin and ingestions of 4 mg can be fatal.

Clinical presentation

- ✓ Intoxication may occur after acute accidental or suicidal ingestion or with chronic therapy.
- ✓ Signs and symptoms depend on chronicity of the intoxication.
- ✓ **With acute over dose:**
  - **vomiting, hyperkalaemia, sinus bradycardia, sinoatrial arrest, and 2nd or 3rd degree AV block** are common.
  - Ventricular tachycardia or fibrillation may occur.
  - **Hyperkalaemia is a marker of severe acute toxicity** and serum potassium is the best predictor of cardiac glycoside toxicity after an acute overdose.
- ✓ **With chronic intoxication**:
  - **visual disturbances, weakness, sinus bradycardia, atrial fibrillation** with slowed ventricular response rate or junctional escape rhythm, and **ventricular arrhythmias** (ventricular bigeminy or trigeminy, ventricular tachycardia, bidirectional tachycardia, and ventricular fibrillation) are common.
  - Accelerated junctional tachycardia and paroxysmal atrial tachycardia with block are frequently seen.
  - Hypokalemia and hypomagnesemia from chronic diuretic use may be evident and appear to worsen the tachyarrhythmias.

Complications

- ✓ Hypoxic seizure
- ✓ Encephalopathy

- ✓ Ischemic stroke
- ✓ MI
- ✓ ATN

Investigation

- ✓ Electrolytes → Serum potassium levels higher than 5.5 meq/L are associated with severe poisoning, serum magnesium
- ✓ BUN & creatinine
- ✓ ECG monitoring
- ✓ Ix based on cxn (if there)
- ✓ Specific levels: stat serum digoxin or digitoxin levels are recommended, although they may not correlate accurately with severity of intoxication. Therapeutic levels of digoxin are 0.5-2 ng/mL; of digitoxin, 10-30 ng/mL.

Treatment

- ✓ ***Emergency and supportive measures:***
- o ABC of life
- o Monitor the patient closely for at least 12—24 h after significant ingestion because of delayed tissue distribution.
- ✓ ***Decontamination:***
- o **Prehospital:** activated charcoal, if there is no contraindication
- o **Hospital:** activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly. Repeat-dose activated charcoal maybe useful for Digitoxin toxicity and in patients with severe renal insufficiency, in which clearance of digoxin is markedly diminished.

- ✓ Treat **hyperkalemia** (refer under short case of Nitsibin. click here → Hyperkalemia)
- ✓ Treat **bradycardia** or **heart block:**
- o **atropine** is usually the drug of choice in this circumstance.
- ➢ For adults, give 0.5-1mg iv. For children, give 0.02 mg/kg iv up to a maximum of 0.5 mg and 1 mg in adolescents. Repeat as needed.
- ➢ Note that 3 mg is a fully vagolytic dose in adults. If response is not achieved at 3 mg, the patient is unlikely to benefit from further treatment unless bradycardia is caused by excessive cholinergic effects (e.g., carbamate or organophosphate overdose).
- o **A temporary pacemaker** may be needed for persistent symptomatic bradycardia.
- ✓ **Treat Ventricular tachyarrhythmias:**
- o may respond to **lidocaine.**
- ➢ Administer 1-1.5 mg/kg (usual adult dose 50-100 mg; children, 1 mg/kg) iv bolus at a rate of 25-50 mg/min, followed by infusion of 1-4 mg/min (20-50 mcg/kg/min) to maintain serum concentrations of 1.5-5 mg/L.
- ➢ If significant ectopy persists after the initial bolus, repeat doses of 0.5 mg/kg iv can be given if needed at 10-min intervals (to a maximum 300 mg or 3 mg/kg total dose; children may be given repeat 1 mg/kg doses every 5-10 min to a maximum of 5 mg/kg).
- o In patients with congestive heart failure or liver disease, use half the recommended

maintenance infusion dose of lidocaine or use phenytoin (a loading dose of 15—20 mg/kg iv slowly at a rate not to exceed 50-100 mg/min or 1 mg/kg/min in children) or to correction of low potassium or magnesium.

- o Avoid quinidine, procainamide, and bretylium.
- ✓ ***Specific drugs and antidotes:***
- o **Digi bind** (Fab fragments of digoxin-specific antibodies)

- ➢ They are indicated for
    - **(acute)** significant poisoning (e.g., severe hyperkalaemia i.e. K>6.0mEq/L, symptomatic arrhythmias not responsive to drugs described above)
    - chronic toxicity with any life-threatening dysrhythmia
    - possibly for prophylactic treatment in a massive oral overdose with high serum levels.
- ➢ Digi bind rapidly binds to digoxin and, to a lesser extent, digitoxin and other cardiac glycosides.
- ➢ The inactive complex that is formed is rapidly excreted in the urine.
- ➢ A full neutralizing dose of digoxin-Fab is based on an estimation of the total-body load of digoxin, which can be calculated from either the dose ingested or a steady-state serum digoxin level.
- ➢ In an acute poisoning, each vial of digoxin-Fab reverses approximately 0.5 milligram of ingested digoxin.
- ➢ In hemodynamically stable patients, half the calculated full neutralizing dose is infused, and the other half is given if an adequate clinical response is not seen in 1 to 2 h.
- ➢ **A total of 200 to 480 mg of digoxin-Fab (5 to 12 vials) is required to effectively treat severely digoxin-toxic patients.**
- ➢ **When the ingested dose is unknown and serum level is unavailable, 10 vials are recommended as initial treatment in life-threatening situations.**
- ➢ **Digoxin-Fab are administered iv through a 0.22-mm filter over 30 min, except in cardiac arrest, when the dose is given as an IV bolus.**

4.4.4 Opiates and opioids overdose

- ✓ This group includes **naturally occurring opiates** (e.g., morphine, heroin, codeine, and hydrocodone) as well as **synthetic opiate analogues** (e.g., fentanyl, pethidine/ meperidine, and methadone.
- ✓ **Dextromethorphan** is an opioid derivative with potent antitussive but no analgesic or addictive properties.
- ✓ **Tramadol** is a newer analgesic that is **unrelated chemically** to the opiates but acts on mu (μ) opioid receptors.
- ✓ Some newer fentanyl derivatives have potency for toxicity up to 2000 times that of morphine.

Clinical presentation

- ✓ **With mild or moderate overdose:**
- o lethargy is common.

- The pupils are usually small, often "pinpoint" size.
- Hypotension and bradycardia
- Diminished bowel sounds
- the muscles are usually flaccid.
- ✓ **With higher doses:**
- In general, opioids have effect in the CNS, causing coma (sedation) and respiratory depression.
- Death results from respiratory failure, usually because of apnea or pulmonary aspiration of gastric contents.
- In addition, acute noncardiogenic pulmonary edema may occur by unknown mechanisms, often after resuscitation and administration of the opiate antagonist naloxone.
- ✓ **Seizures** occur occasionally with certain compounds
- ✓ **Cardiotoxicity•**
- ✓ Opioid **withdrawal syndrome** can cause anxiety, piloerection (goose bumps), abdominal cramps, diarrhoea, and insomnia.
- ✓ **typical manifestations** of opiate intoxication are pinpoint pupils, respiratory and CNS depression, and the patient quickly awakens after administration of naloxone.
- ✓ Signs of iv drug abuse (e.g., needle track marks) may be present.

Investigation

- ✓ RBS
- ✓ Electrolytes
- ✓ CXR
- ✓ arterial blood gases or oximetry

Treatment

- ✓ *Emergency and supportive measures:*
- ABC of life
- Administer supplemental oxygen.
- Treat coma, seizure, hypotension and non-cardiogenic pulmonary edema if they occur.
- ✓ *Decontamination:*
- **Prehospital:**
    - provide general supportive care.
    - Activated charcoal is generally not indicated because of the risk of aspiration.
    - Do *not* induce vomiting because of the potential for developing lethargy and coma.
- **Hospital:**
    - Administer activated charcoal if a patient presents soon after ingestion and is not manifesting signs of toxicity. It is not recommended in patients showing signs of toxicity because of the risk of aspiration.
    - Gastric emptying is not necessary if activated charcoal can be given promptly.

- ✓ *Specific drugs and antidotes:*

- **Naloxone,** 0.4—2 mg, IV, repeat doses every 2—3 min, if there is no response, up to a total dose of 10—20 mg
  - **It is a specific opioid antagonist**
  - large doses may be given safely.
  - As little as 0.2—0.4 mg is usually effective for heroin overdose.
  - *Caution:* the duration of effect of naloxone (1—2 h) is shorter than that of many opioids. Therefore, do not release the patient who has awakened after naloxone treatment until at least 3—4 h have passed since the last dose of naloxone.
  - In general, if naloxone was required to reverse opioid-induced coma, it is safer to admit the patient for at least 6— 12 h of observation.
- **Sodium bicarbonate** may be effective for QRS interval prolongation or hypotension associated with propoxyphene poisoning.

4.4.5 Phenothiazines and other antipsychotic drug overdose

- ✓ Phenothiazines, butyrophenones, and other related drugs are widely used to treat psychosis and agitated depression.
- ✓ In addition, some of these drugs (e.g., prochlorperazine, promethazine, and triperidol) are used as antiemetic agents.
- ✓ Suicidal overdoses are common, but because of the high toxic-therapeutic ratio, acute overdose seldom results in death.

Clinical presentation

- ✓ Major toxicity is manifested in the cardiovascular and CNS.
- **CVS toxicity:** tachycardia, orthostatic hypotension.
- **CNS toxicity:** CNS depression, small pupils, Extrapyramidal dystonic reactions, disturbed, Temperature regulation resulting in poikilothermia
- ✓ **Mild intoxication:**
- causes sedation, small pupils, and orthostatic hypotension.
- Anticholinergic manifestations include dry mouth, absence of sweating, tachycardia, and urinary retention. Paradoxically, clozapine causes hypersalivation through an unknown mechanism.
- ✓ **Severe intoxication:**
- may cause coma, seizures, and respiratory arrest.
- Hypothermia or hyperthermia may occur.
- Clozapine can cause a prolonged confusion state and rarely cardiac toxicity.
- ✓ **Extrapyramidal** dystonic side effects of therapeutic doses include torticollis, jaw muscle spasm, oculogyric crisis, rigidity, bradykinesia, and pill-rolling tremor.
- ✓ Patients on chronic antipsychotic medication may develop the **neuroleptic malignant syndrome** characterized by rigidity, hyperthermia, sweating, lactic acidosis, and rhabdomyolysis.
- ✓ Clozapine use has been associated with agranulocytosis

Investigation

- ✓ RBS
- ✓ Electrolytes
- ✓ BUN &creatinine
- ✓ CPK
- ✓ arterial blood gases or oximetry
- ✓ abdominal x-ray → to look for radiopaque pills, Phenothiazines are occasionally visible on plain abdominal x-rays
- ✓ chest x-ray
- ✓ ECG → usually shows QT interval prolongation and occasionally QRS prolongation (particularly with thioridazine and Risperidone).

Treatment

- ✓ ***Emergency and supportive measures:***
- o ABC life and supplemental oxygen.
- o Treat coma, seizures, hypotension, and hyperthermia if they occur.
- o Monitor vital signs and ECG for at least 6 h and admit the patient for at least 24 h if there are signs of significant intoxication.
- ✓ ***Decontamination:***
- o **Prehospital:** general supportive measures. Administer activated charcoal if there is no contra indication. **Do *not induce* vomiting**.
- o **Hospital:** consider activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly
- ✓ **There is no specific antidote.**
- ✓ **Dystonic reactions:** give diphenhydramine, 0.5—1 mg/kg IV/IM or benztropine.
- ✓ **QRS interval prolongation:** treat quinidine-like cardiotoxic effects with bicarbonate, 1-2 mEq/kg IV.

4.4.6 Benzodiazepines (BDZ) Toxicity

- ✓ BDZ's to varying degrees, **have in common 6 major pharmacologic effects**: **Sedative, hypnotic, anxiolytic, amnestic, anticonvulsant and muscle relaxant**.
- ✓ BDZ's are commonly used for the short-term treatment of anxiety, insomnia, seizures, and alcohol and sedative-hypnotic withdrawal.
- ✓ Examples of BDZ's include; **diazepam**, lorazepam, midazolam, alprazolam, temazepam, triazolam, clonazepam…
- ✓ Isolated benzodiazepine overdose has no significant morbidity and mortality. Most serious toxicity will occur in the setting of co-ingestion of other agents or with parenteral administration.
- ✓ Death due solely to benzodiazepine overdose is rare in otherwise healthy individuals.
- ✓ Deaths in seemingly isolated overdoses are more likely with short-acting derivatives such as alprazolam, temazepam, and triazolam.

Clinical Features

- ✓ nonspecific
- ✓ **The predominant manifestations are neurologic** and are characterized by somnolence, dizziness, slurred speech, confusion, ataxia, incoordination, and general impairment of intellectual function.
- ✓ **Coma**, particularly if prolonged, **is atypical** and should prompt suspicion of intoxication with other agents or a non-toxin—related medical condition.
- ✓ In the elderly, infants and children, protein-deficient persons, and those with hepatic disease, the neurologic effects of benzodiazepines may be prolonged or enhanced.
- ✓ Paradoxical reactions, including excitement, anxiety, aggression, hostile behavior, rage, and delirium, are quite uncommon.
- ✓ Other effects that have unclear aetiologies include headache, nausea, vomiting, chest pain, joint pain, diarrhea, and incontinence.
- ✓ Some benzodiazepines may cause short-term anterograde amnesia.
- ✓ Uncommonly, respiratory depression and hypotension may occur
- ✓ Extrapyramidal reactions.
- ✓ Various allergic, hepatotoxic, and hematologic reactions are infrequent.
- ✓ In general, benzodiazepines have no long-term organ-system toxicity other than that which can be ascribed to indirect effects from neurologic or cardiorespiratory depression.

Investigations

- ✓ RBS →.to rule out hypoglycemia as the cause of chane in mentation.
- ✓ CBC
- ✓ RFT
- ✓ LFT with Liver enzymes
- ✓ Pregnancy test in women of childbearing age
- ✓ ECG → to rule out conduction system poisoning by drugs that effect the QRS or QTc interval
- ✓ Arterial blood gas analysis

Management

- ✓ ***Initial treatment***
- ○ ABC of life → Endotracheal intubation if needed. Oxygen, secure IV line, continuous cardiac monitoring.
- ○ Check RBS immediately
- ○ vast majority of benzodiazepine overdoses can be managed expectantly.
- ○ Activated charcoal is generally not beneficial in overdose.
- ✓ **Antidote →** ***Flumazenil***
- ○ The initial adult dose of flumazenil is 0.2 mg (In children, 0.01 mg/kg, up to 0.2 mg), IV over 30 seconds.
- ○ A second dose of 0.3 mg may be given, followed by 0.5-mg doses at 1-minute intervals, to a total of 3 mg.
- ○ Most patients respond within 3 mg.

- Because the duration of action of flumazenil is short (0.7—1.3 hours), re sedation occurs in up to 65% of patients and requires either re dosing or continuous infusion (0.25—1.0 mg/hr)
- Flumazenil is a nonspecific competitive antagonist of the benzodiazepine receptor, **can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and overdose, but is not recommended for the reversal of benzodiazepine overdose in the ED.**
- **Seizures and cardiac dysrhythmias can occur with flumazenil administration, and fatal**

Flumazenil		
Indication	*Contraindications*	
	Absolute	*Relative*
✓ Isolated benzodiazepine overdose in nonhabituated user (e.g., accidental pediatric exposure) ✓ Reversal of conscious sedation	✓ Known or suspected co-ingestant that lowers seizure threshold ✓ TCA, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate ✓ Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures) ✓ Concurrent sedative-hypnotic withdrawal ✓ Seizure activity or myoclonus ✓ Hypersensitivity to flumazenil or benzodiazepines ✓ Patient with neuromuscular blockade	✓ Chronic benzodiazepine user, not taking for control of life-threatening condition ✓ Known seizure disorder not treated with benzodiazepines ✓ Head injury ✓ Panic attacks ✓ Chronic alcoholism

✓ **Disposition**

- Patients remaining asymptomatic after 4 to 6 hours of ED observation may be medically cleared.
- For cases of deliberate overdose, appropriate psychiatric consultation should be obtained
- Indications for observation or hospital admission include significant alterations in mental status, respiratory depression, and hypotension.
- If mental status depression persists or is profound, other agents or conditions must be considered.

4.4.7 Anticonvulsants poisoning

4.4.7.1 Phenytoin and fos phenytoin poisoning

✓ Phenytoin is a primary anticonvulsant for partial and generalized tonic clonic seizures.

- ✓ Serious complications are extremely rare after intentional phenytoin overdose if supportive care is provided.
- ✓ Most phenytoin-related deaths have been caused by rapid IV administration or hypersensitivity reactions.
- ✓ Phenytoin is extensively (about 90%) bound to plasma proteins, especially albumin.
- ✓ The free, unbound form is responsible for the drug's clinical effect and toxicity.
- ✓ The unbound fraction of the drug is greater in neonates, the elderly, pregnant women,
  renal failure, hypoalbuminemia (cirrhosis, nephrosis, malnutrition, burns, trauma), and hyperbilirubinemia.
- ✓ Drugs that displace phenytoin from binding sites (salicylate, valproate, phenylbutazone,
  tolbutamide, and sulfisoxazole) also result in an increased unbound fraction.
- ✓ **Fosphenytoin** (a disodium phosphate ester of phenytoin) is a prodrug that is converted to phenytoin by phosphatases in the body

Clinical manifestations

- ✓ ***CNS Toxicity***
- o **Nystagmus** → The initial sign of toxicity, which is seen first on forced lateral gaze and later becomes spontaneous. Vertical, bidirectional, or alternating nystagmus may occur with severe intoxication. But, absence of nystagmus does not exclude severe phenytoin toxicity.
- o lethargy, ataxic gait, and dysarthria.
- o confusion, coma, and even apnea in a large overdose.
- o complete ophthalmoplegia and loss of corneal reflexes.
- o Paradoxically, very high levels of phenytoin may be associated with seizures, although this is a rare occurrence, and such phenytoin-induced seizures are usually brief and generalized and almost always are preceded by other signs of toxicity, especially in acute overdose.
- o Dystonias and movement disorders, such as opisthotonos and choreoathetosis.
- o Hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited.
- o Chronic neurologic toxicity includes peripheral neuropathy and cerebellar degeneration with ataxia.

- ✓ ***CVS Toxicity***
- o CVS CXN have been almost entirely limited to cases of IV administration, or in rare cases of chronic oral toxicity.
- o CVS toxicity is more common in the elderly, those with underlying cardiac disease, and the critically ill patients.
- o hypotension
- o bradycardia
- ✓ ***Vascular and Soft Tissue Toxicity***
- o IM injection of *phenytoin* may result in hematoma, sterile abscess, and myonecrosis at the injection site.
- o IV extravasation may produce skin and soft tissue necrosis, compartment syndrome,

and limb gangrene.
- o Delayed bluish discoloration of the affected extremity ("purple glove syndrome") followed by erythema, edema, vesicles, bullae, and local tissue ischemia

- ✓ ***Hypersensitivity Reactions***
- o Hypersensitivity reactions usually occur within 1 to 6 weeks of beginning phenytoin therapy and can present as a febrile illness with skin changes (**erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson syndrome**) and internal organ involvement (**hepatitis, rhabdomyolysis, acute interstitial pneumonitis, renal failure, LAP, leukopenia and/or DIC**).
- o Patients with a history of previous hypersensitivity reactions should not receive phenytoin
- ✓ ***Miscellaneous Effects***
- o **Gingival hyperplasia is relatively common** and is associated with poor dental hygiene gingivitis and dental plaques.

Investigation

- ✓ **RBS -** To r/o hypoglycemia as the cause of any alteration in mental status.
- ✓ **CBC**- may have leucocytosis, eosinophilia
- ✓ Elevated **liver enzymes**.
- ✓ **Serum albumin level**- hypoalbuminemia patients with a therapeutic or mildly elevated phenytoin concentration may exhibit significant toxicity.
- ✓ **Pregnancy test-** should be done in women of childbearing age.
- ✓ **Serum Phenytoin level-** The therapeutic phenytoin serum level is 10 to 20 μg/mL which generally corresponds to a free phenytoin level of 1 to 2 μg/mL.
- ✓ **ECG** -reveals increased PR interval, widened QRS interval, and altered ST segments and T waves, arrhythmias, ventricular tachycardia, primary ventricular fibrillation, atrioventricular block, or sinus arrest with junctional or ventricular escape that may occur after intravenous (or very rarely oral) exposure

Management

- ✓ **ABC of life**
- o Endotracheal intubation if indicated
- o Treat Hypotension with IV boluses of isotonic saline. Atropine, epinephrine, and dopamine remain first line medical treatment for symptomatic brady dysrhythmias.
- ✓ **Decontamination**
- o Activated charcoal (AC) may be useful in the setting of a recent ingestion.
- o Multiple dose AC may remove some unbound phenytoin undergoing enterohepatic circulation, even if the phenytoin was administered IV. It is not routinely use multiple doses of activated charcoal.
- ✓ **Seizures** from phenytoin toxicity should be treated with benzodiazepines and barbiturates as needed.
- ✓ **There is no specific treatment or antidote for phenytoin toxicity**
- ✓ **Disposition and Follow-Up**
- o The decision to discharge or medically clear a patient for psychiatric evaluation

should be clinically, cannot be based on one serum level.

  - After acute ingestions, serum level should be measured every few hours.
  - Patients with serious complications after an oral ingestion (seizures, coma, altered mental status, or significant ataxia) should be admitted for further evaluation and treatment.
  - Those with only mild symptoms may be observed in the ED and discharged once their levels of phenytoin are declining.
  - Mental health or psychiatric evaluation should be obtained, as indicated, in cases of intentional overdose.

4.4.7.2 Carbamazepine poisoning

- Carbamazepine is a primary anticonvulsant used in the treatment of partial and tonic clonic seizures. Other uses include trigeminal neuralgia, chronic pain disorders, manic disorder, and bipolar disorder.

Clinical manifestations

- Neurologic and possibly some CVS effects characterize acute carbamazepine toxicity.
- **CNS effects;**
  - The initial neurologic disturbances include nystagmus, ataxia, and dysarthria. In patients with large overdoses, fluctuations in level of consciousness and coma occur.
  - Carbamazepine toxicity may cause seizures in both in epileptic and nonepileptic patients by unknown mechanism.
  - Chronic carbamazepine overdose can result in headaches, diplopia, or ataxia. Idiosyncratic adverse events are common.
- **Cardiovascular** effects
  - include sinus tachycardia, hypotension with myocardial depression, and cardiac conduction abnormalities.
  - These abnormalities can be delayed for as long as 20 hours and may occur with chronic therapy but are not associated with life-threatening dysrhythmias or permanent sequelae.

Investigation

- RBS
- U/A
- CBC
- **Liver enzymes** → elevated in acute toxicity
- **serum electrolyte** → hyponatremia
- **Pregnancy test**- should be done in women of childbearing age.
- **ECG**
  - Carbamazepine can cause QRS prolongation and arrhythmia
  - Sinus tachycardia is the most frequently observed cardiac effect of carbamazepine
  - Other effects include; bradycardia, AV block, premature ventricular contractions, ventricular tachycardia, and junctional escape rhythms

- ✓ **Serum carbamazepine level**
- o should be followed serially in an acute overdose.
- o Serum concentrations may not peak for over 96 hours; levels should be obtained every four to six hours until there is a definite downward trend and the patient is improving clinically.
- o Therapeutic concentrations of carbamazepine range from 4 to 12 µg/mL.
- o Carbamazepine concentrations above 40 mg/mL correlate with an increased risk for apnea, dystonia, hypotension, and coma

Management

- ✓ **ABC of life**
- ✓ **Gastrointestinal decontamination**
- o **Activated charcoal remains the most common method for acute carbamazepine poisoning**
- o Multidose activated charcoal may be used in cases of severe carbamazepine poisoning
- ✓ **Extracorporeal elimination**
- o In patients with severe toxicity and multiorgan dysfunction, **haemodialysis, hemoperfusion, or hemodiafiltration is effective**.
- ✓ QRS prolongation is treated with **sodium bicarbonate**. give boluses of 100 to 150 meq of sodium bicarbonate IV for QRS intervals longer than 110 milliseconds, particularly in patients with hypotension.
- ✓ Seizures caused by carbamazepine overdose should be treated with **GABA agonists**, such as benzodiazepines (eg, lorazepam). Propofol administered as a continuous infusion for the sedation of intubated patients also functions as an effective anticonvulsant. There is **no role** for phenytoin in the management of drug-induced seizures.
- ✓ ECG monitoring may be necessary in some patients
- ✓ Patients can be medically cleared from the ED if at least two carbamazepine measurements obtained a few hours apart show decreasing levels (preferably below 15 µg/mL) and the patient is awake, ambulatory, and free of cardiac conduction abnormalities.

4.4.7.3 Valproate (valproic acid/VPA/) poisoning

- ✓ Valproate (or valproic acid) is used to treat **tonic-clonic seizures, absence seizures, partial complex seizures, and post-traumatic epilepsy.**
- ✓ Valproate is also used in migraine headache prophylaxis, to control **manic episodes in bipolar disorder**, and to treat neuropathic pain.

Clinical features

- ✓ After acute toxicity, the most frequent sign is CNS depression, ranging from

drowsiness to coma.

- ✓ Other findings include respiratory depression, hypotension, hypoglycaemia, and electrolyte disturbances that may persist for days.
- ✓ Anion gap metabolic acidosis following overdose is a poor prognostic sign.
- ✓ Bone marrow suppression occurs 3—5 days following acute massive overdoses of VPA and is characterized by pancytopenia. These hematopoietic disturbances usually resolve spontaneously within a few days.
- ✓ Hepatotoxicity → Valproate-induced hepatotoxicity may be either intrinsic and benign (reversible, reproducible, and dose dependent) or idiosyncratic and fatal (unpredictable, not dose dependent, with a long latent period).
- ✓ Pancreatitis may occur, and thrombocytopenia may be clinically significant and severe.
- ✓ Cerebral edema has been seen in acute overdose.

Investigations

- ✓ **RBS** → hypoglycaemia as cxn of toxicity or to rule out hypoglycaemia as the cause of any alteration in mental status
- ✓ **U/A-**Valproate is eliminated partly as ketone bodies and may cause a positive test result for ketones in the urine or blood.
- ✓ **Urine HCG** -in women of childbearing age
- ✓ **CBC-** as a baseline and to see complication of VPA toxicity (Pancytopenia, thrombocytopenia)
- ✓ **Serum electrolyte**-hypernatremia, hypocalcaemia, hypophosphatemia, and anion gap metabolic acidosis can be complication of valproate poisoning
- ✓ **LFT and Enzyme tests-** To see hepatotoxicity (elevated serum levels of aminotransferases, ammonia, and lactate)
- ✓ **ECG-** to rule out conduction system impairment by drugs that prolong the QRS or QTc intervals
- ✓ Lipase and amylase- To assess Acute pancreatitis
- ✓ Serum ammonia level → Hyperammonaemia in the absence of liver failure during long-term therapy.
- ✓ Arterial blood gas analysis- To See anion gab metabolic acidosis and treat accordingly
- ✓ Serum acetaminophen and Salicylates level-to rule out these common congestions
- ✓ **Serum valproic acid concentration**
  - o Therapeutic valproate concentrations are 50 to 100 μg/mL.
  - o Although serum concentration does not correlate well with either seizure control or toxicity, **adverse side effects increase as concentrations rise above 150 μg /mL, and coma may occur with levels above 800 μg /mL.**
  - o A consistent analytic methodology should be used when monitoring treatment.

Treatment

- ✓ **Single-dose activated charcoal alone is sufficient for the vast majority of patients with a valproate overdose.**
- ✓ Consider multidose activated charcoal and/or whole-bowel irrigation after ingestion of

enteric coated, delayed-release preparations to prevent the ongoing absorption that may occur from delayed capsule or tablet dissolution.

- ✓ Because of delayed peak serum levels after an overdose, serial concentrations should be measured.
- ✓ high-dose naloxone to reverse valproate-induced neurologic depression, But naloxone is unlikely to be helpful in the management of a comatose patient after valproate overdose.
- ✓ Hemoperfusion and hemodiafiltration have been used to treat severe valproate overdose.
- ✓ **Disposition and follow up**
- ○ **Patients with signs or symptoms (eg, somnolence) of severe VPA poisoning are admitted to an ICU.**
- ○ In addition, adult patients who ingest > 200 mg/kg of VPA and/or have plasma concentrations > 180 µg/mL (1260 µmol/L) usually develop some degree of CNS depression and warrant admission to a closely monitored setting.
- ○ **Asymptomatic patients who ingest immediate-release preparations should be observed closely for 6 hours.**
- ○ If the VPA level is low and the patient remains asymptomatic, further clinical deterioration is highly unlikely.
- ○ **Patients who ingest sustained-release preparations should be observed for at least 12 hours.**

4.4.8 Barbiturates (Commonly phenobarbitone/PB/)

- ✓ Barbiturates are from the group of ‘sedative — hypnotics’ that lower excitement & induce sleep.
- ✓ **Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening.**
- ✓ While tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.
- ✓ The main action of barbiturates is to depress activity in the nervous and musculoskeletal systems.
- ✓ **Barbiturates act directly on the medulla to produce respiratory depression.**

Clinical features

- ☛ **Mild barbiturate toxicity mimics ethanol intoxication, presenting with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional liability, and impaired cognition.**
- ☛ In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest.
- ☛ **The life threat of severe barbiturate toxicity is respiratory depression**
- ☛ **A characteristic of a barbiturate overdose is the persistence of the pupillary light reflex even with stage IV coma.** Although pupils are usually normal or small and reactive, concomitant

hypoxia can cause pupils to be fixed and dilated.

- Corneal and gag reflexes may be diminished or absent
- muscle tone flaccid, and DTR diminished or absent.
- Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose.
- These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma.
- A fluctuating level of consciousness is commonly seen.
- Bullous skin lesions often occur over the hands, buttocks and knees.
- Barbiturate overdose has been associated with non-cardiogenic pulmonary edema.
- Other Common complications include hypoglycaemia (perhaps due to starvation), aspiration pneumonia, and acute lung injury.
- Most common vital sign abnormalities are:
  — Hypothermia
  — Respiratory depression
  — Hypotension

Investigations

Routine lab. Investigations

- RBS
- CBC
- RFT, LFT, serum electrolyte
- Arterial blood gas (if indicated)

Imaging

- CXR→ can detect noncardiogenic pulmonary edema or pneumonia.
- CT of the head → should be obtained in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis

EEG → Since the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared “brain dead” if barbiturates are present at therapeutic levels or greater.

Toxicology screen

- **Barbiturate serum levels:**
  - Useful for the diagnosis of a comatose patient; however, acute treatment decisions should be clinically based.
  - The therapeutic level of phenobarbital is 15 to 40 µg/mL (65—172 µmol/L).
  - A serum level > 50 µg/mL can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80 µg/mL are potentially fatal.

Treatment

1. ABCDE Assessment and Initial Stabilization •

- Mechanical ventilation and intubation in severe overdose before GI decontamination.
- Volume expansion, by rapid infusion of **1-2 L of isotonic fluid,** is the mainstay of circulatory support in the absence of cardiac failure. If fluid resuscitation fails to correct hypotension, vasopressors such as dopamine and norepinephrine should be initiated.
- Check hypoglycaemia and treat
- Hypothermia between 30°C (86°F) and 36°C (96.8°F) is common and should be treated with rewarming measures.

2. Decontamination

- With very large overdoses, antecedent **gastric lavage** may be considered.
- A single dose of **activated charcoal** should be given to cooperative, clinically stable patients who present with in 1 hour of acute oral overdose. For patients who have a compromised airway, endotracheal intubation is advised prior to giving charcoal
- **Multi-dose activated charcoal is consider if a patient has ingested a life-threatening amount** of phenobarbital.
- monitor the airway is to decrease the risk of aspiration or bowel obstruction.

3. Urinary Alkalinization → It is not considered a first-line treatment for phenobarbital poisoning and **it is not effective for shorter-acting barbiturates.**

4. Extracorporeal Elimination

- Haemodialysis, hemoperfusion, and hemodiafiltration have all been used to enhance elimination of phenobarbital; however, they are **reserved for patients who are deteriorating despite aggressive supportive care.**
- **These modalities are not useful for poisoning from barbiturates other than phenobarbital.**
- Exchange transfusion has also been reported useful in neonatal phenobarbital toxicity

Disposition and Follow-Up

- Mild to moderate barbiturate intoxication responds well to general supportive care, including a single dose of activated charcoal, if appropriate.
- Improvement in neurologic status and vital signs over 6 to 8 hours signals eventual patient discharge or transfer.
- When indicated, assessment by mental health services should be performed or arranged.
- For phenobarbital, a long-acting agent, serial serum levels should be obtained during the initial 6 hours after an overdose before concluding the patient can be safely discharged or transferred.
- Evidence of toxicity after 6 hours will require hospital admission, and patients with severe toxicity should go to the intensive care unit.

4.4.9 TCA (Tricyclic antidepressant) Poisoning

- ✓ TCA consists of: amitriptyline, clomipramine, desipramine, imipramine, amoxapine and maprotiline.
- ✓ Life-threatening ingestion at >10mg/kg, and fatalities at >1gm for adults (therapeutic dose 5-10mg/kg/day).
- ✓ Prolonged GI absorption due to anticholinergic effects.

Clinical features:

- ✓ **Mild to moderate overdose/ toxicity,** anti-muscarinic effect predominates and presentation includes:
  - o **Central effect:** agitation, confusion, hallucination, seizure, ataxia, drowsiness, sedation, coma
  - o **Peripheral:** dry skin and mucosa, mydriasis, tachycardia, mild hypertension, hyperthermia, Urinary retention, ileus, tremor, myoclonus, hyperreflexia
- ✓ **Severe toxicity:** usually occurs within 6 hours if ingestion, consist of: Coma, cardiac conduction delays, supraventricular and ventricular tachycardia, hypotension, Respiratory depression, seizure.
- ✓ In summary TCA poisoning may produce any of the three major toxic syndromes: **anticholinergic effects, cardiovascular effects and seizure disorder**.
- ✓ **Secondary complications** include, **Aspiration pneumonia, pulmonary edema, anoxic encephalopathy, hyperthermia, rhabdomyolysis** can contribute to morbidity and mortality.
- ✓ **Death from TCA overdose may result from ventricular fibrillation, intractable cardiac shock, or status epileptics and from secondary complications**.

ECG Features

- ✓ The classic ECG with TCA toxicity shows
  - o sinus tachycardia, right axis deviation, and prolongation of the PR, QRS, and QT intervals
  - o less commonly aBrugada pattern (incomplete RBBB with ST elevation in V1-3 leads) and various block type.
  - o ECG abnormalities develop within 6 hours of ingestion and typically resolve over 36 to 48 hours.
- ✓ The following signs suggest cardio toxicity:
  - o Prolongation of the QRS >100 msec
  - o Abnormal morphology of the QRS (eg, deep, slurred S wave in leads I and AVL)
  - o Abnormal size and ratio of the R and S waves in lead AVR: R wave in AVR >3 mm; R to S ratio in AVR >0.7

Management of TCA overdoses

- ABCs and supportive management
  - ✓ Secure double IV line
  - ✓ Monitored setting, full set of vital signs,
  - ✓ serial ECG
  - ✓ Airway equipment available
  - ✓ Intubate if low LOC or respiratory depression
  - ✓ Hyperventilate to pH of 7.50-7.55
  - ✓ Provide high-flow oxygen
  - ✓ **If hypotensive (shock)**
    - o give NS, IV boluses in increments of 10 mL/kg to a maximum of 30 mL/kg.
    - o Hypotension that does not improve with appropriate fluid challenges should be treated with sodium bicarbonate (regardless of QRS complex duration).
    - o Vasopressors (Norepinephrine and epinephrine) should be used when hypotension is unresponsive to fluids and sodium bicarbonate therapy
    - o Vasopressin can be tried if there is no response to norepinephrine or epinephrine.
    - o Dopamine is less effective than norepinephrine
  - ✓ Do NOT treat hypertension
  - ✓ Urinary catheterization to prevent urinary retention, and a nasogastric tube may be needed if ileus is present.
- Universal antidotes → "TONG", Thiamine, Oxygen, Naloxone (opioid antagonist), Glucose
- GI Decontamination → After the ABC's have been secured and If pt comes within 1hr of ingestion but also later if severe toxicity
  - ✓ Activated charcoal
  - ✓ Gastric lavage (in intubated patient) → if ingested >20mg/Kg
  - ✓ Don't induce emesis
- Treat seizures with:
  - IV diazepam 5-10mg
  - May use phenobarbital, propofol
  - Avoid phenytoin (Na+-channel blocker)
- Alkalinisation and Na loading for dysrhythmia by
  - ✓ Sodium bicarbonate → also Used to treat cardiac conduction abnormalities (the above ECG features)
  - ✓ Hypertonic NACl (3%,7%)

Disposition

- Patients with an alteration in mental status, hypotension, cardiac conduction abnormalities, or seizures should be admitted to ICU.
- Patients with mild symptoms, such as an isolated tachycardia without evidence of conduction abnormalities (i.e., QRS <100 msec), could conceivably be admitted to a monitored bed/ setting.
- Asymptomatic patients who have no conduction abnormalities on ECG, may deteriorate rapidly and should be monitored for at least 6 hours in an acute care setting can be safely discharged or transferred to a psychiatric service for evaluation.
- Hospitalized patients can be cleared medically after 24 hours if they are asymptomatic,

with a normal or baseline ECG, normal mental status, and resolution of all antimuscarinic symptoms.

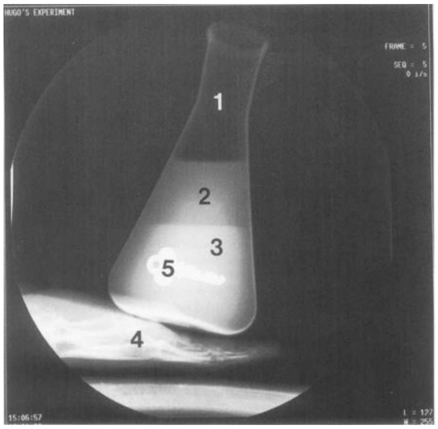
Chapter 5; Interpretation of Chest X - Ray (የደረት ራጅ ማንበብ)

Dr. Mulualem. G

- A CXR is a two-dimensional representation of a three-dimensional structure. As a result, the CXR includes many overlapping structures

Basic principles: Densities

- The more X-rays reach an area of the film, the darker that area will be on the radiograph. Therefore, if an object is very dense, less X-rays will reach the film and consequently the image of the object will appear white on the radiograph.
- If an object has little density, its image will appear black on the CXR because it allows most of the X-ray beam to reach the film.
- Difference in density and x ray attenuation…help outline anatomic structures…allowing visualization of details



Image; Plain films have five basic radiographic densities in order of increasing brightness: 1 → Air (black), 2 → Fat (gray), 3 → Fluid (gray), 4 → Bone (white), 5 → Metal or x ray contrast agents (white).

Basic stapes for Interpretation of CXR

A. Quality Assessment (Technical Aspects)
   - Is the film correctly labeled?
   - Assessment of exposure quality

B. Assessment of Patient dependent factors
   - Assessment of Centering / Symmetry of film:
   - Assessment of adequacy of inspiratory effort

C. Review of important radiographic anatomy
   - The soft tissues
   - Bony structures (Ribs, sternum, thoracic spine, clavicle, scapula)
   - The diaphragm → Elevation, flattening, costophrenic (C-P) angle, air under the diaphragm
   - The pleura:
   - Trachea
   - The Hilum
   - The lung fissures
   - The lungs
   - The Heart and mediastinum

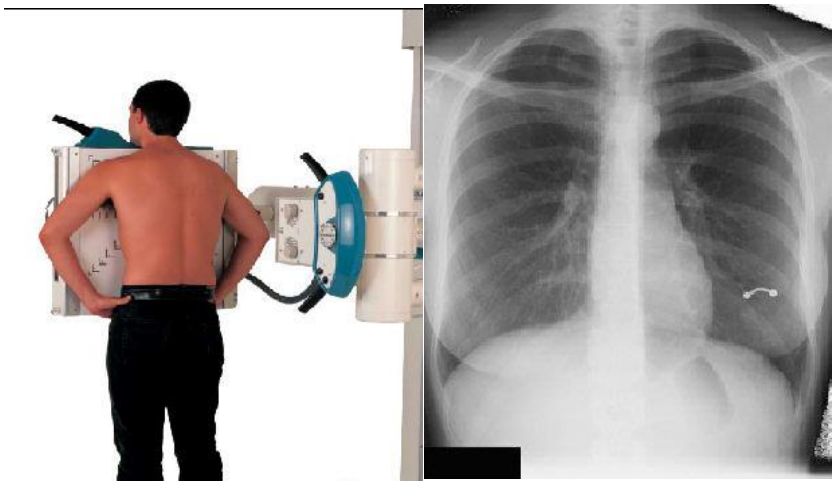
5.1 Step 1. Quality Assessment (Technical Aspects)

1.1 Is the film correctly labeled? Check the following:

- Name, age and sex of the patient
- Date of CXR is taken
- Health facility's name
- The left & right-side markers
- Projection of film
    - P-A: commonly used
    - A-P…. "ward film"
    - Lateral
    - Lateral decubitus

CXR Projections

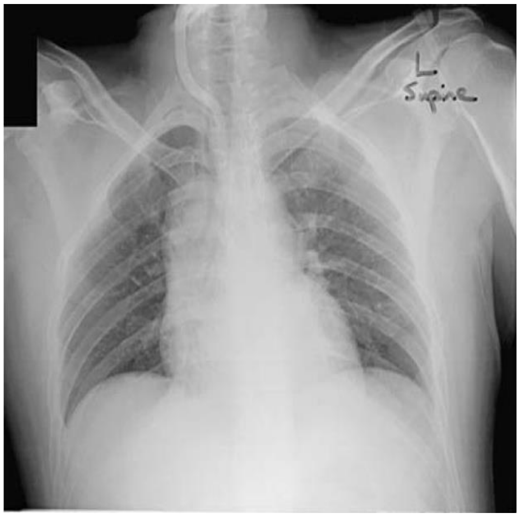
A) P-A projection



Figure; **PA CXR;** Most CXRs are taken in a PA position; The x-ray beam passes through the patient from back to front (i.e. PA) onto the film. The heart and mediastinum are thus closest to the film and therefore not magnified.

B) A-P or supine film

- Portable bedside CXR- “ward film”, Especially for critically ill / ICU pts
- Important to;
    - Look for new pathology after admission
    - Assess C-P status & position of catheters, ETTs and other devices
    - Detect complications related to these devices

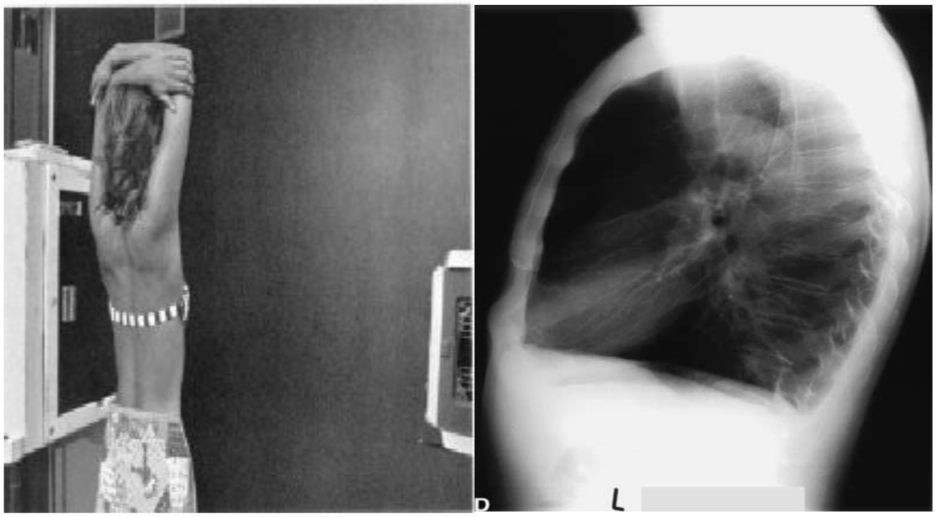


Image; A-P CXR

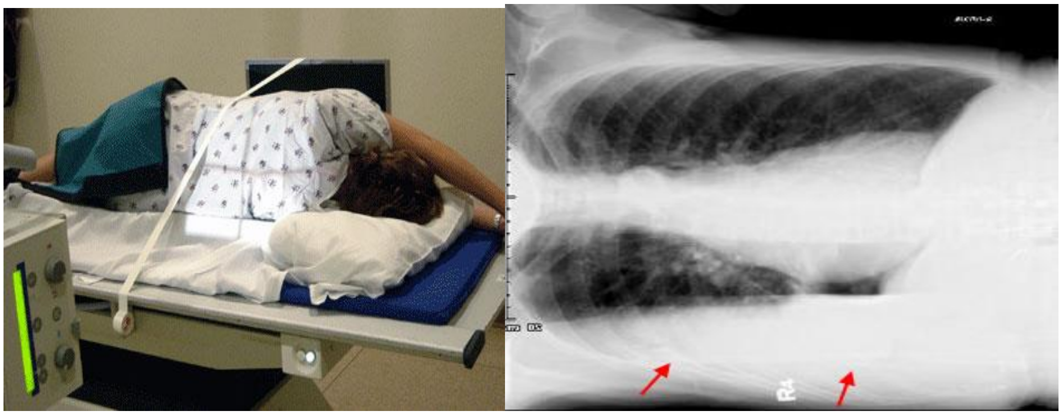
- Limitations:
    - Often rotated films, poor quality

- Magnification of intra thoracic structures
    - Widening of upper mediastinum…due to increase in venous return
    - Cardiac diameter increased by 15-20%
    - High position of diaphragm
    - Small lung volumes, compression of lower lobes
- Difficult to detect small pleural effusions and pneumothorax

C. lateral view



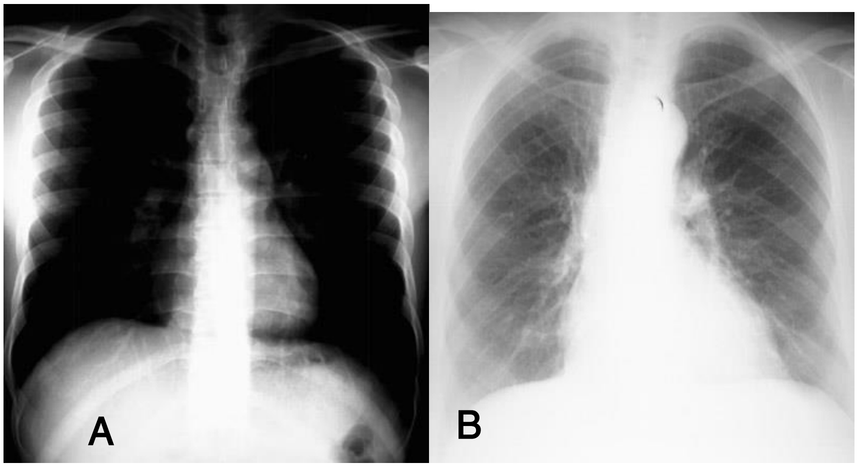
D. Lateral Decubitus



1.2 Assessment of exposure quality:

- Is the film penetrated enough?
- In Optimal exposure /good penetration
    - Vertebrae are seen until T4 spine; below which it is covered by cardiac shadow. T4 is at the level of sternal angle

  - Visualization of vessels to at least 1/3rd of the lung periphery.

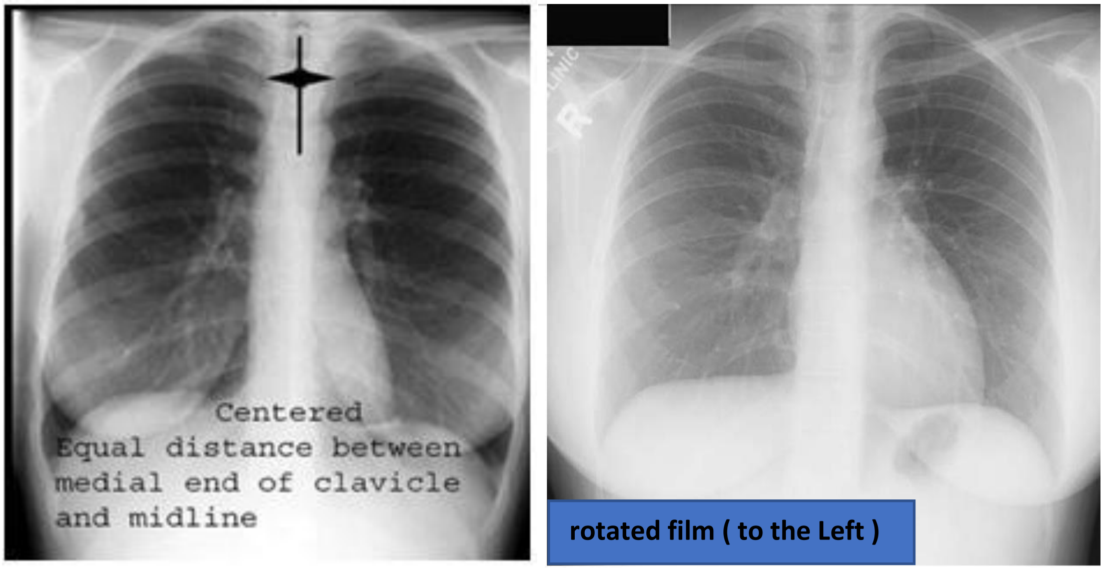


Picture; A) Over penetrated/ over exposed film (Dark film). Easy to see thoracic spines behind the heart shadow; but pulmonary vessels peripherally are not clearly seen. B) Under penetrated film (The image too white); Fail to see vertebrae above T4 (and also behind the heart). Accentuates pulmonary vascularity, which may be mistaken for generalized infiltrates.

5.2 Step 2. Assessment of Patient dependent factors

2.1 Assessment of Centering / Symmetry of film:

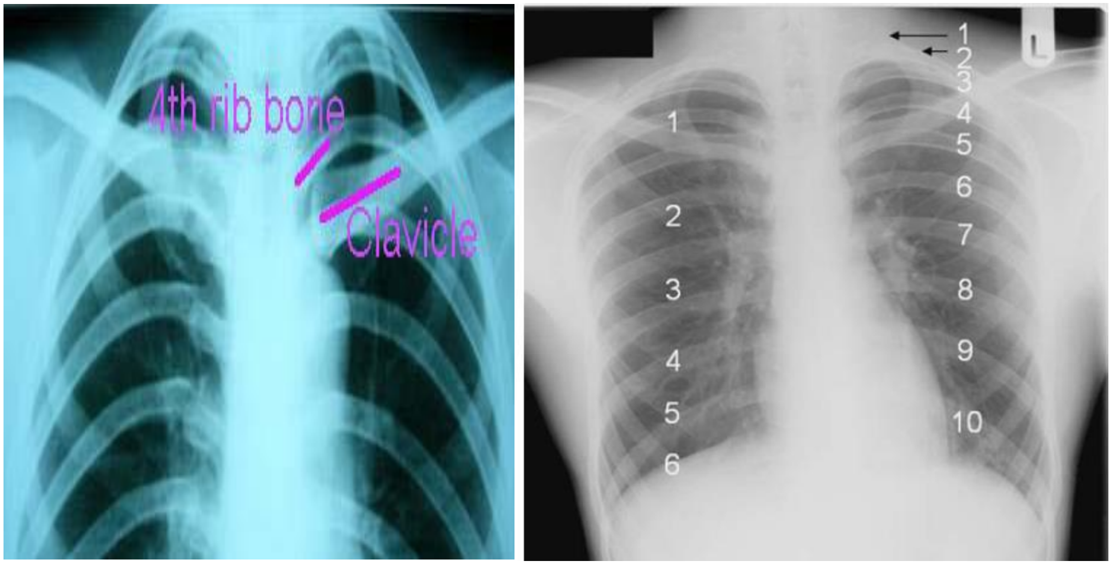
- Well centered CXR: medial / sternal ends of clavicles are equidistant from the mid line (the vertebral spinous process)
  - If distance on one side is > 1.5 cm, it is asymmetric
  - Patient rotation to one side makes the side of lung darker.
- If there is rotation, the side to which the patient is rotated is assessed by comparing the densities of the two hemi-thoraces. The increase in blackness of one hemi-thorax is always on the side to which the patient is rotated, irrespective of whether the CXR has been taken PA or AP.
- Rotation will also alter the relative appearance on the hila and can mimic hilar asymmetry and the projection of the sternum over the hilum may be evident


Centered
Equal distance between
medial end of clavicle
and midline
R
rotated film (to the Left)

Picture; this patient (image over the right) is rotated to the left. Note the spinous process is close to the right clavicle and the left lung is 'darker' than the right, due to the rotation.

2.2 Assessment of adequacy of inspiratory effort (i.e. does the patient has taken adequate inspiratory effort?)

- By counting visible anterior or posterior ribs


4th rib bone
Clavicle
L
1
2
3
4
5
6
1
2
3
4
5
6
7
8
9
10

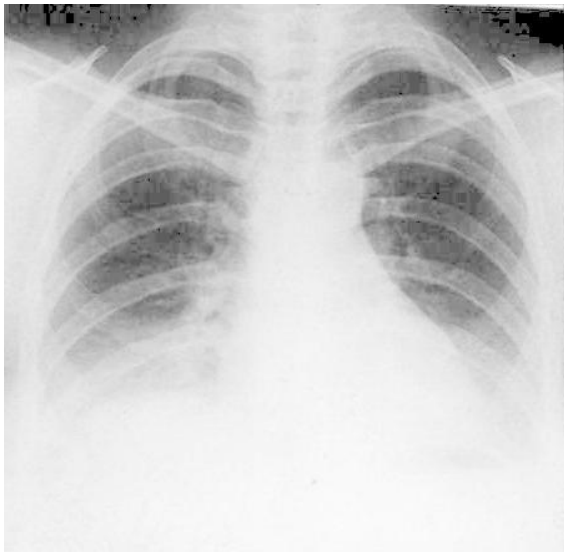
Picture; Optimal: 6 anterior or 10 posterior ribs are visible above the diaphragm

Poor inspiratory effort / Expiratory film:

CXR is taken on expiration

- Hemidiaphragms are higher
- Small and dense lung volumes

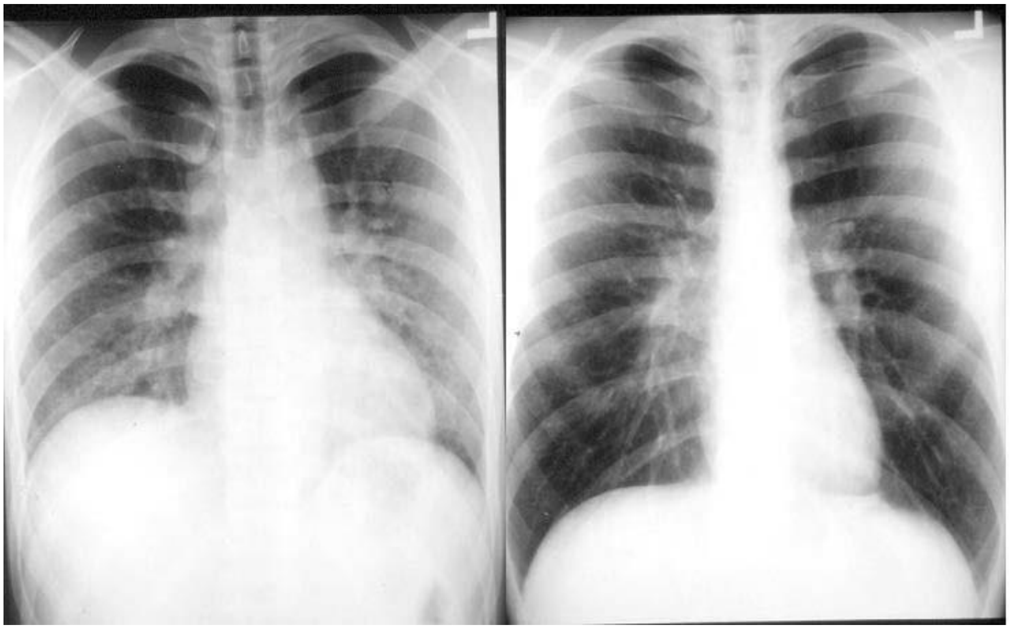
- Heart appears large, crowding of basilar pulmonary vessels.
- Breast shadows overlap the hemi diaphragms.
- Expiratory film obtained after maximum expiration to RV
    - To detect air trapping, small pneumothorax



Picture; < 6 anterior or < 10 posterior ribs visible

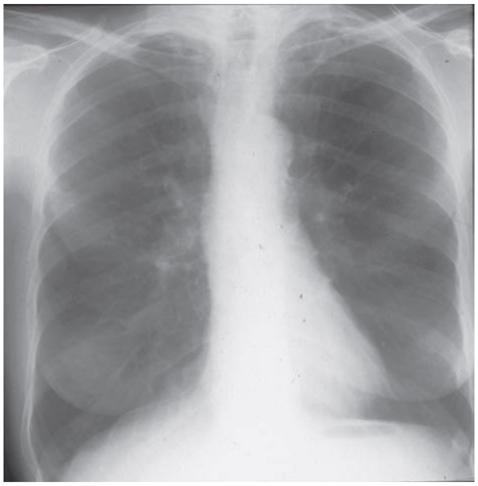
- Limitations: Results in spurious findings like
    - Enlarged cardiac silhouette
    - Bilateral patchy basilar infiltrates
    - Hilar or mediastinal abnormalities
- Misinterpreted as cardiomegaly, basal pneumonia/interstitial lung diseases.

Poor inspiratory effort Vs full inspiration



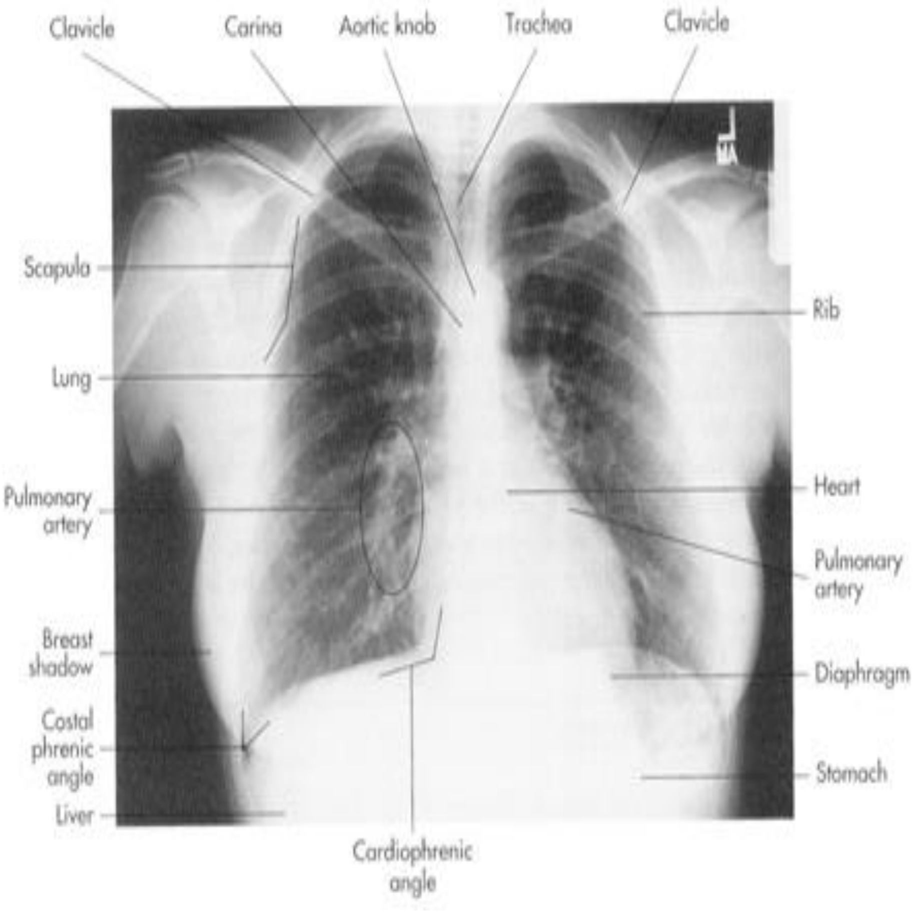
Picture; Two CXRs of the same patient taken on the same day. For the CXR on the left the patient has made a poor inspiratory effort. Note the apparent bulkiness of the hila, increased density in the lower zones and the enlarged cardiac silhouette. The CXR on the right taken in full inspiration demonstrates that the patient's CXR is normal and previous apparent abnormalities were due to poor inspiratory effort

- If > 6 anterior or > 10 posterior ribs are visible above diaphragm, it implies hyperexpanded lungs (eg. air trapping as in COPD with large lung volumes & flat diaphragm)

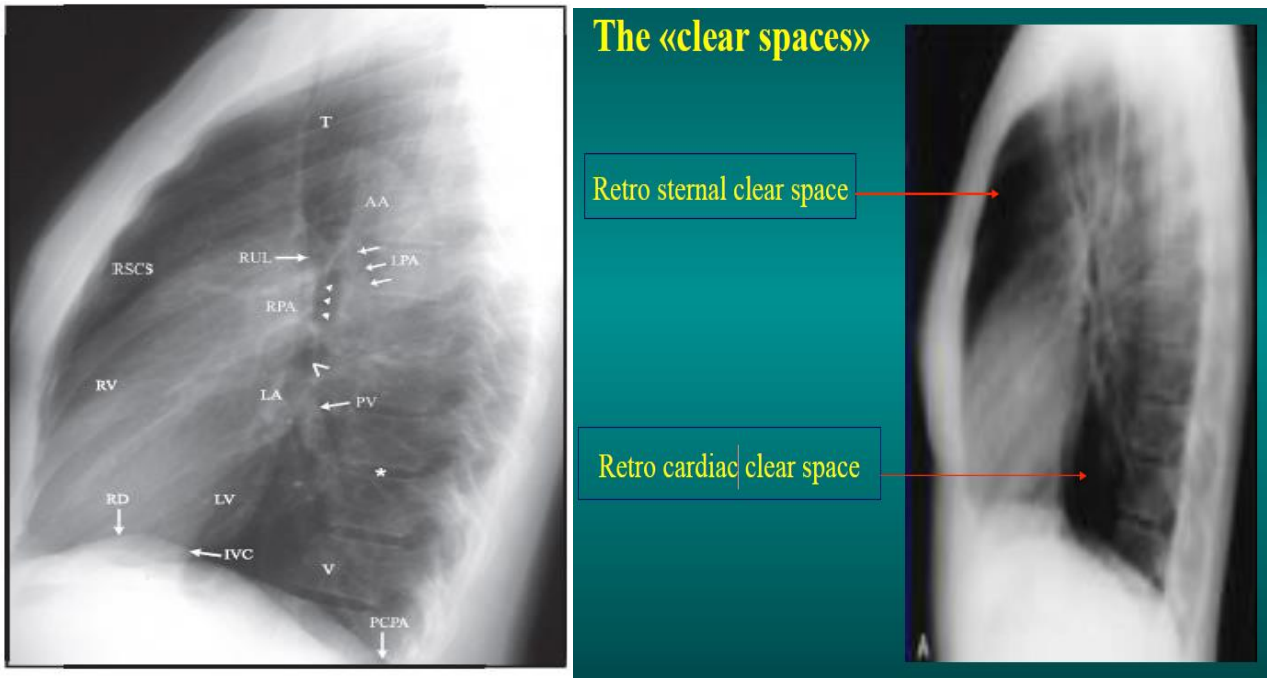


5.3 Step 3. Review of important radiographic anatomy

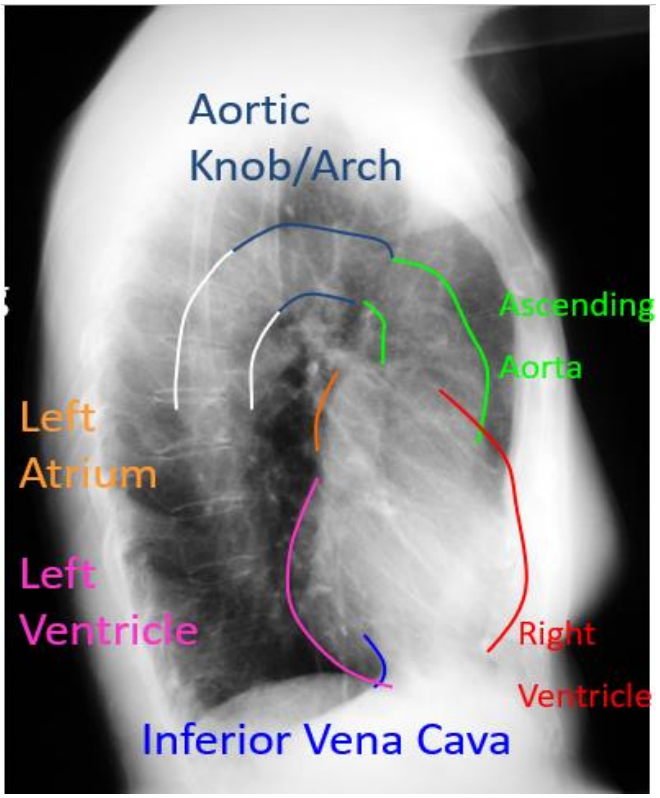
- From the periphery to the center or vice versa.
- Compare symmetrical sides of the film


Clavicle
Carina
Aortic knob
Trachea
Clavicle
Scapula
Rib
Lung
Pulmonary artery
Heart
Pulmonary artery
Breast shadow
Diaphragm
Costal phrenic angle
Stomach
Liver
Cardiophrenic angle

- Review areas:
    - Apices
    - Behind the heart
    - CP angles
    - Below the diaphragm
    - Soft tissues (breast, surgical emphysema)
    - Ribs & clavicle
    - Vertebrae
- Hidden areas: apices, mediastinum & hila, posterior sulcus

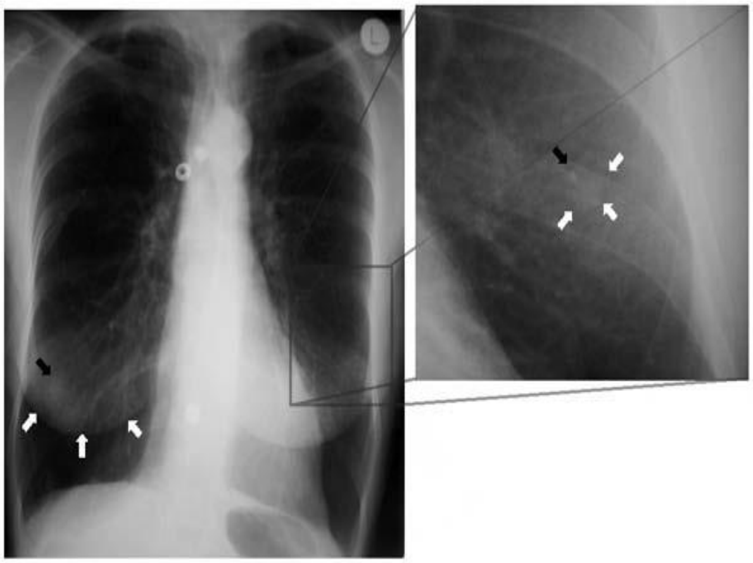

T
AA
RUL
LPA
RSCS
RPA
RV
LA
PV
*
RD
LV
IVC
V
PCPA
The «clear spaces»
Retro sternal clear space
Retro cardiac clear space

Pictures; Normal lateral CXR, PCPA- post C_A angle


Aortic Knob/Arch
Ascending Aorta
Left Atrium
Left Ventricle
Right Ventricle
Inferior Vena Cava

3.1 The soft tissues

- Normal tissue shadowing on CXR -breast shadow, nipple shadow
- Look for any subcutaneous emphysema, edema, or mass
- The soft tissues lateral to the bony thorax should be smooth, symmetric homogeneous densities



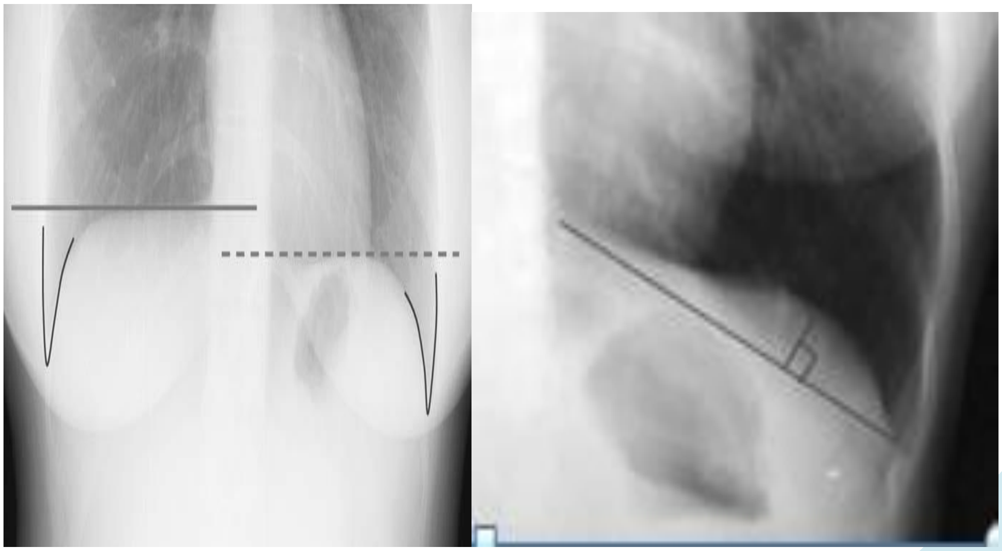
Picture; Breast and nipple shadow

3.2 Bony structures

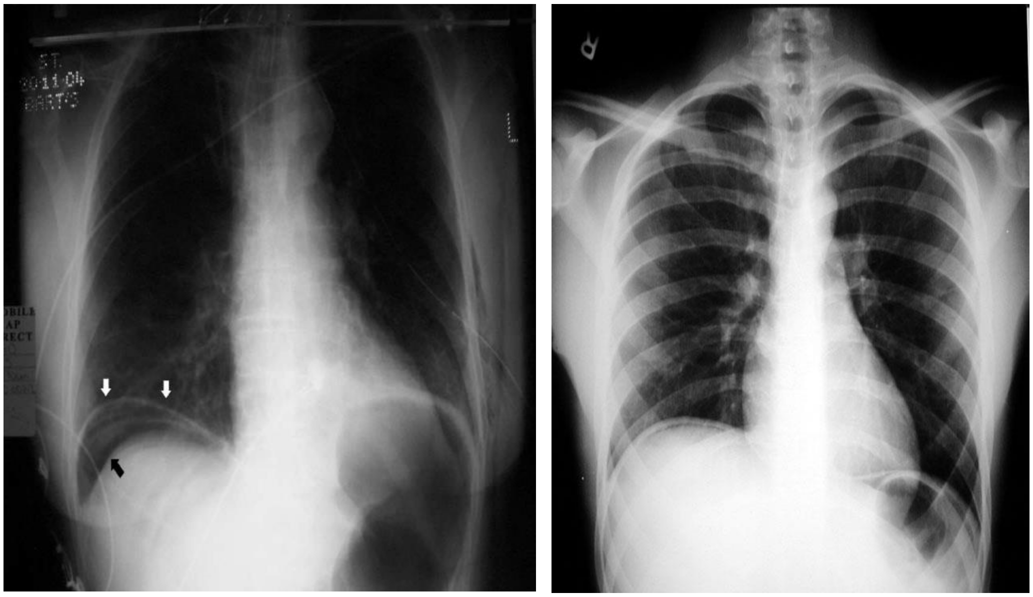
- (Ribs, sternum, thoracic spine, clavicle, scapula)
- look for any bone mass or lesion (lytic, sclerotic), fracture, deformity, rib spacing, notching etc.

3.3 Diaphragm

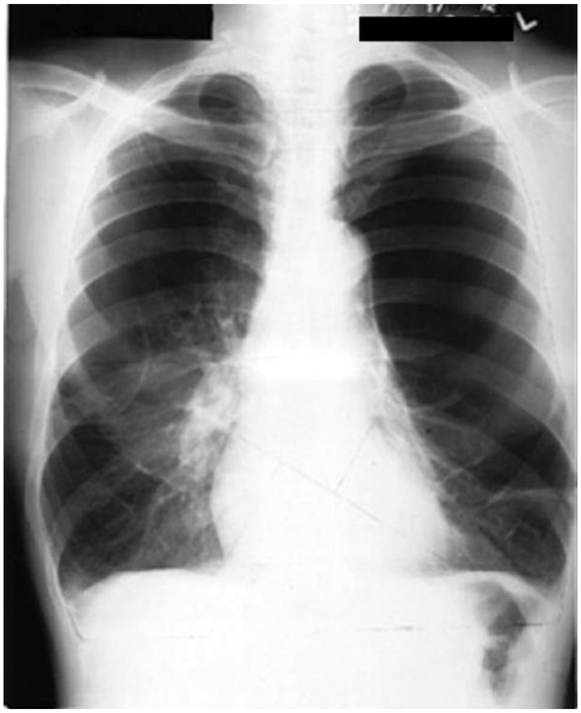
- Elevation, flattening, C-P angle, air under the diaphragm
- Normally the Right is higher (by 1-1.5cm) than the Left. A difference of > 3cm is abnormal
- The highest point of the hemidiaphragm should be at least 1.5cm above a line drawn from cardio phrenic to costophrenic angle (< 1.5 cm suggests flat diaphragm)
- Air in the gastric fundus is normally seen below Left hemidiaphragm but air under Right hemidiaphragm is pathological (as in perforated PUD).



Dome medially located with a sharp costophrenic angle



Picture; Air under the diaphragm, the normally air-filled gastric fundus lies beneath the diaphragm. If there is free gas on the left, only the diaphragm, about 3—4 mm thick, separates the free gas from the lung. Air in the gastric fundus is separated from the lung by the diaphragm and the gastric wall. Again, sharp margins to the gas shadow increase the likelihood of free gas. If uncertainty remains, a lateral decubitus AXR view should resolve the issue, as the free gas will travel to the least dependent area, i.e. the upper most lateral margin of the abdomen.

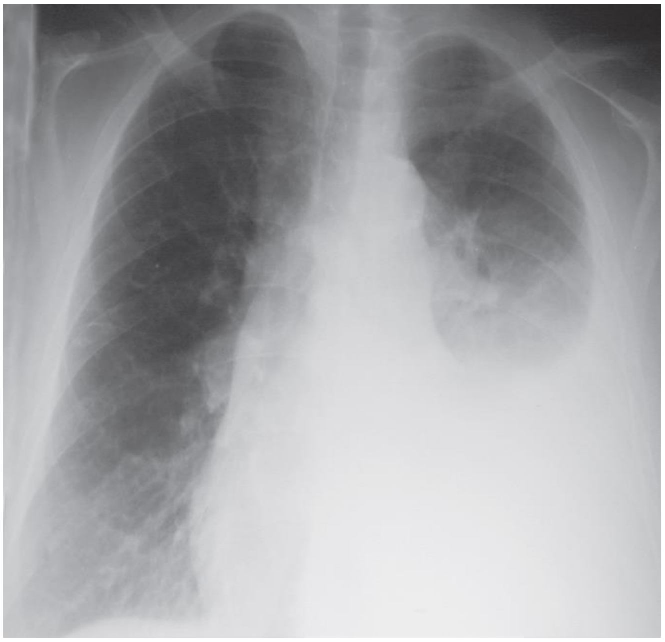


Picture; Emphysema: see the flat diaphragm

3.4 Pleura

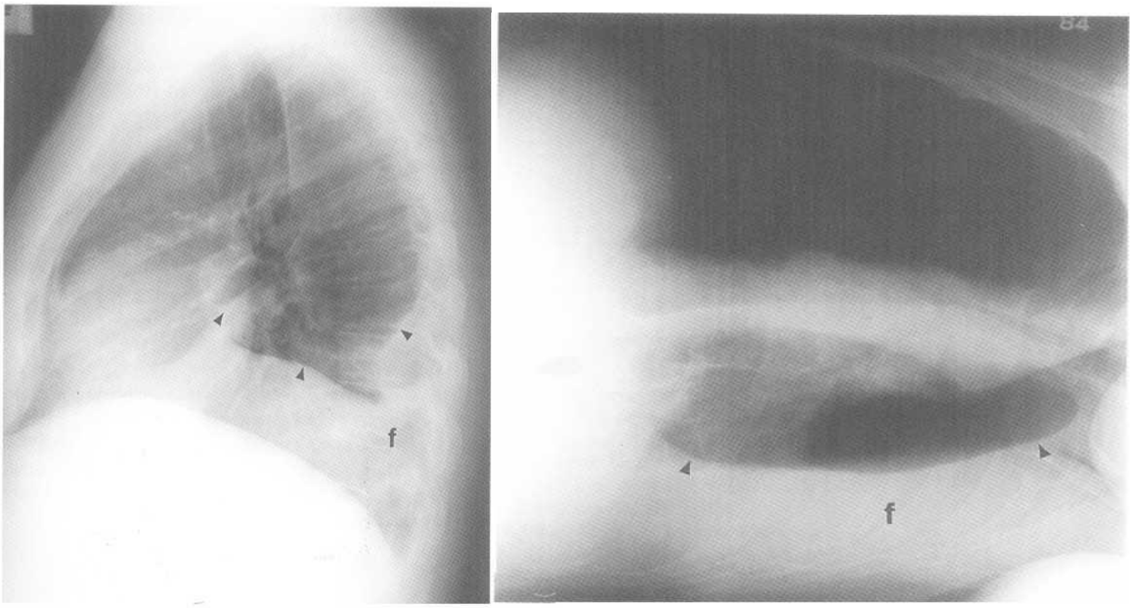
Look for

- Fluid or air in the pleural cavity; thickening, calcification
- Normally the costophrenic angle is acute. Obliteration tells pleural effusion/empyema
- Meniscus sign (◡) is the typical obliteration of the costophrenic angle suggesting fluid in the pleural cavity.
- 250ml fluid can be detected on a PA film; lateral decubitus film can detect 10 to 50 ml. The smallest amount visible on decubitus radiographs is 10 ml. With care, as little as 175 mL of effusion can be detected on supine images.



Picture; Pleural effusions show homogeneous opacity without air bronchogram (as the pleura is extra parenchymal). This helps to differentiate pleural fluid from consolidation.

- In the supine position, a simple pleural effusion will accumulate posteriorly in the chest and the above described meniscal effect is not seen.
- On an upright PA film, fluid collects in the lateral costophrenic angle due to gravity, giving it a blunted appearance. The posterior costophrenic angle is the deepest, and fluid collects there first. This angle is hidden by the dome of the diaphragm on a PA view. However, it is well seen on the lateral view. For this reason, the upright lateral view is superior to the PA for demonstrating small amounts of pleural fluid.
- When in doubt of pleural effusion, order a decubitus view with the patient lying down on the side of the suspected effusion. This will bring the fluid between the lung and the chest wall where it is easy to see. Sometimes the parietal and visceral pleura are stuck to each other (adhesion). In this situation, a pleural effusion may not be able to move when the patient changes position. The fluid may even be stuck in one of the fissures mimicking the appearance of a lung mass (pseudo-tumor).
- Immobile pleural fluid is called a loculated effusion.



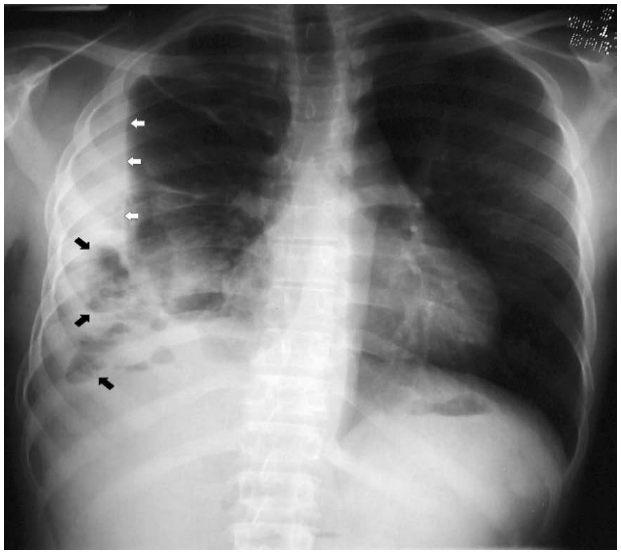
B C

Pictures; B) Lateral CXR: fluid around the left lower lobe. C) Left lateral decubitus view: fluid between the chest wall and the left lung. A free fluid separating the lung from chest wall by > 10 mm on lateral film is an indication for therapeutic thoracentesis.

- Pleural fluid 1st spill out to posterior C-P angle, then to lateral & eventually anterior; with further accumulation, it spreads up wards. Appear as Homogenous opacity obscuring the basal lung field, Obliteration of the costophrenic and cardio phrenic angle, Elevation of the ipsilateral hemidiaphragm

a. Empyema

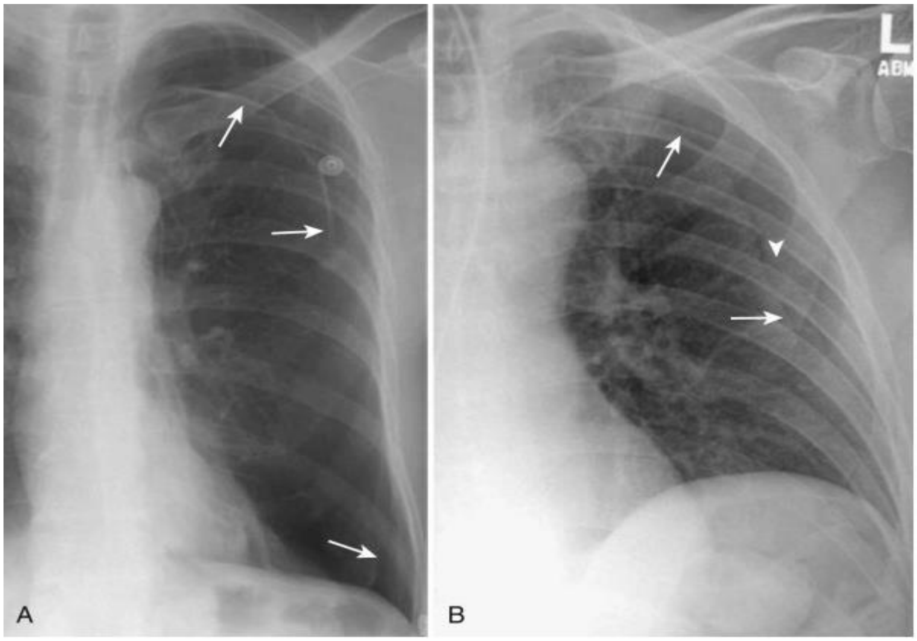
- Presents as a complex pleural collection.
- Fibrous bands may create loculations and the thicker fluid/pus may not be mobile, therefore failing to collect in the dependent areas
- Meniscal contour may not be seen



Picture; Frontal CXR of an adult with a right sided empyema. Note the pleural based opacity with a vertical (white arrows) rather than meniscal contour indicating a complex collection in this case including pockets of air (black arrows). The presence of pleural opacity that fails to conform to the meniscal appearance characteristic of a simple pleural effusion should alert the reader to the possibility of an empyema, or pleural tumor. Extension of an empyema outside the chest wall may mimic an invasive soft tissue mass

b. Pneumothorax

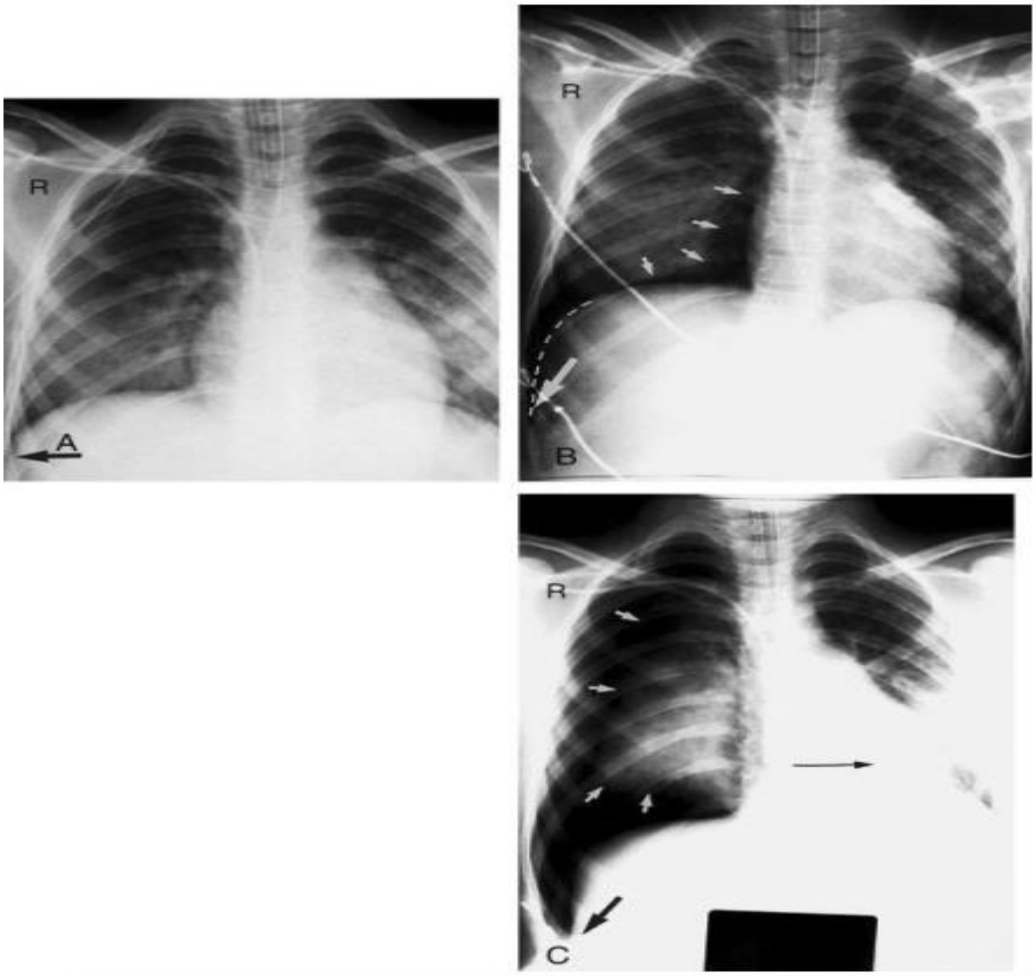
- Best seen on expiratory films
- In upright PA film, look for a black crescent over the apex of the lung.
  - The visceral pleura is often seen as a thin white line under the black crescent, since it is flanked by air on each side
  - No lung tissue (branching white blood vessels) is seen peripheral to the visceral pleura line



Picture; A) Chest radiograph of a pneumothorax. The pleural line has lucency on either side, representing air in the pleural space on one side of the line and air in the lung on the other. The line is sharply demarcated and can be traced along its course (lower arrow). No blood vessels can be seen beyond the superior (upper arrow) and lateral (middle arrow) extent of the line. B) Chest radiograph of a skinfold (arrows) that could be mistaken for a pneumothorax. The border is more of an edge, with lucency on only one side. The edge is poorly defined and cannot be followed continuously (lower arrow). Blood vessels can be traced beyond the border of the fold (arrowhead). A skin-fold line often is relatively straight, whereas a pleural line follows the curve of the inner aspect of the chest wall

Deep sulcus sign of pneumothorax

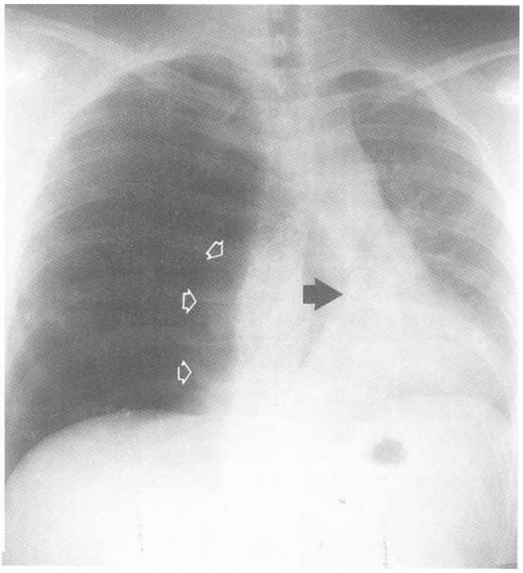
- On a supine AP, the air rises to the anterior and lateral costophrenic angles (sulci); since they are the highest region in the pleural cavity when pt is lying down. This creates an abnormally dark and deep lateral sulcus (i.e. deep sulcus sign).



Picture; On P-A chest x-ray (A), the costophrenic angle is normally acute (arrow). In a supine patient, a pneumothorax will often be anterior, medial, and basilar. On a subsequent supine film (B), the dark area along the right cardiac border and lung base appeared larger (small arrows), and the costophrenic angle much deeper and more acute than normal (large arrow). These findings were not recognized, and, as a result, a tension pneumothorax developed in the same patient (C) with an extremely deep costophrenic angle (large black arrow), an almost completely collapsed right lung (small white arrows), and shift of the mediastinum to the left.

c. Tension pneumothorax

- It is a medical emergency and pt may present with cardiorespiratory distress which needs immediate intervention

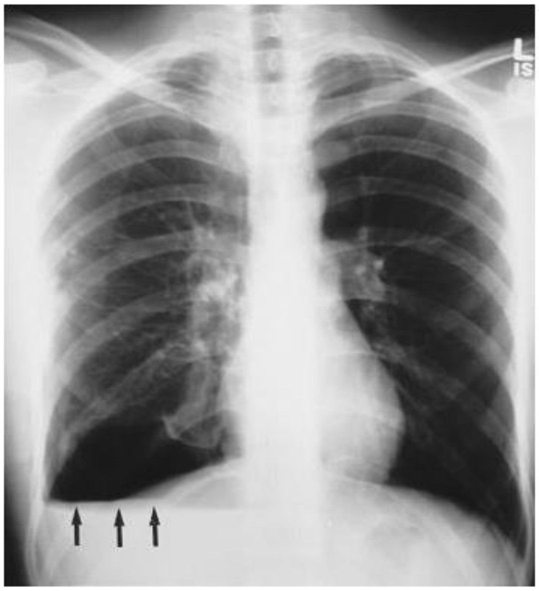


B

Picture; PA CXR demonstrating an abnormally black right hemithorax. The right lung has been pushed medially. The mediastinum is shifted to the left

d. Hydropneumothorax

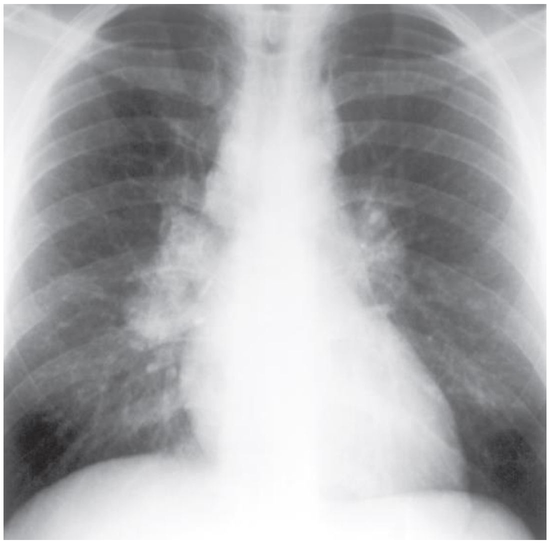
- Presence of both gas & fluid in pleural space
  - On erect CXR —air fluid level
  - Loculated form - appear as single or multiple collection with air fluid level



Picture; Hydropneumothorax. When fluid and air are present in the pleural space on an upright chest x-ray, a perfectly straight horizontal line will extend all the way from the spine to the edge of the pleural cavity. In this patient, a loculated right basilar hydropneumothorax is present. The air/fluid interface is easily seen (arrows). If this were a lung abscess, the air/fluid level would be very unlikely to extend all the way from the medial to the lateral aspect of the hemithorax

3.5 Trachea

- Normally mid line or slightly shifted to the right
- Diameter is 25mm in male, 21mm in female
- Look for:
    - Any narrowing, widening
    - Displacement: away from the side of a pneumothorax or effusion; towards in fibrosis or collapse
    - Carinal angle — site of bifurcation of trachea, located at T6. Normal angle is 60^0 - 75^0. Angle increased in Left Atrial enlargement or LAP
    - Right paratracheal stripe: Normally the Right wall of the trachea should be clearly seen (uniformly smooth and < 4mm in width)
    - Any thickening or nodularity



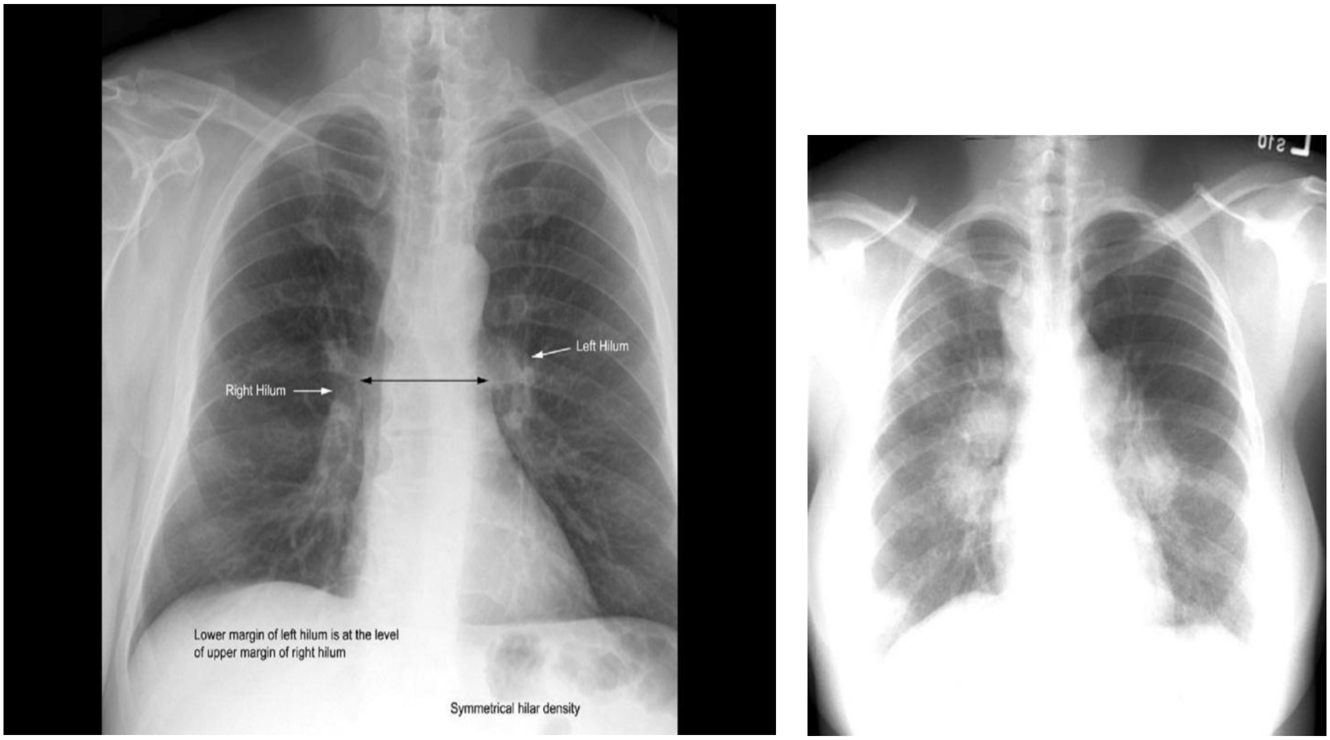
Picture; Rt paratracheal stripe thickening & bilateral hilar enlargement

- The left lateral tracheal wall is surrounded by mediastinal vessels and fat is not normally visible on CXR
- The hilar point is formed by the outer margins of the upper lobe pulmonary veins and the lower lobe pulmonary arteries as they cross. Note the left main pulmonary artery loops over the left main bronchus therefore the left basal pulmonary artery crosses the left upper lobe pulmonary vein higher on the left than on the right and the hila point is also normally higher on the left.

3.6 Hilum

- Formed by pulmonary vessels and adjacent airways
- Normally LNs are not seen on a CXR
- Equal density, size & concave lateral border

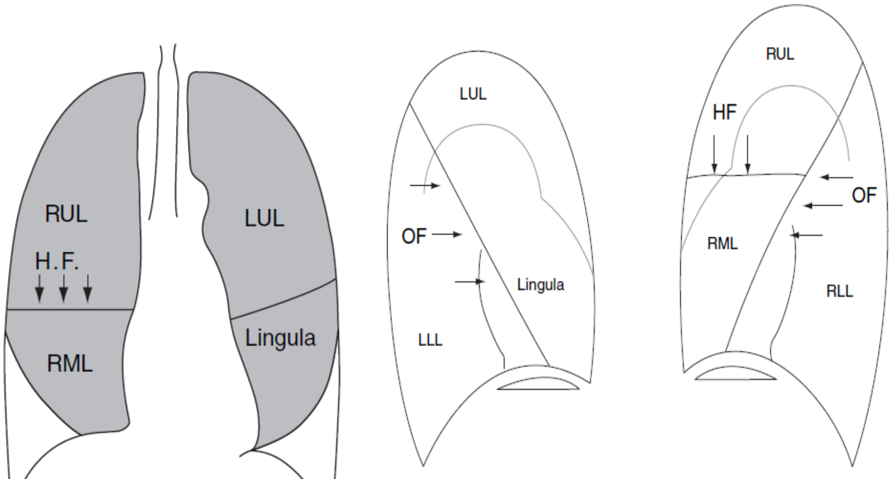
- Y shaped on its side appearance.
- Left hilum is 1 - 2.5 cm higher than the right.
- Hilar prominence occurs in: TB, sarcoidosis, lymphoma, fungal disease, pneumoconiosis, lung ca & metastases, Pulmonary arterial hypertension


Left Hilum
Right Hilum
Lower margin of left hilum is at the level of upper margin of right hilum
Symmetrical hilar density

Picture; Sarcoidosis; Symmetrical hilar nodes, Paratracheal nodes, AP window nodes, Alveolar lung infiltrate

3.7 Lung fissures

- Fissures are pleural reflections which separate the individual lobes.
- The right lung has oblique (major) and horizontal (minor) fissures.
- The left lung has an oblique fissure, separating it into upper and lower lobes.
- Note: The horizontal fissure is seen on both frontal and lateral views as a fine horizontal line. The oblique fissures are seen only on the lateral film as oblique lines.


RUL
H.F.
RML
LUL
Lingula
LUL
OF
Lingula
LLL
RUL
HF
OF
RML
RLL

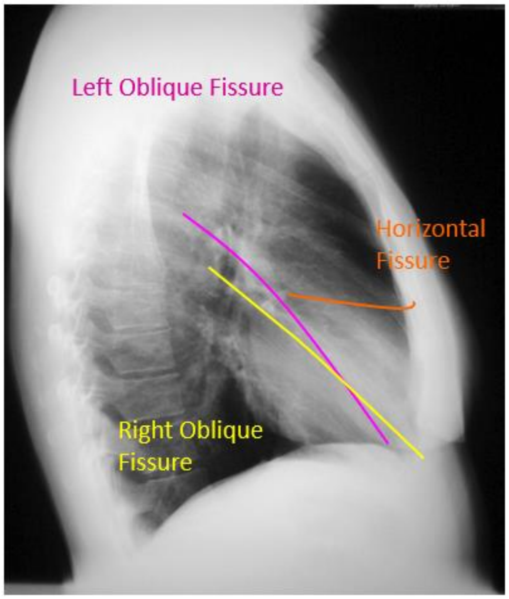
Lobar and pleural anatomy – left lateral view.

Lobar and pleural anatomy – right lateral view.

Picture; Main Fissures; Right upper lobe (RUL) sits above horizontal fissure (HF), the Right lower lobe (RLL) lies behind the oblique fissure (OF) and Right middle lobe (RML) is between the two. left lung has an oblique fissure, separating it into left upper lobe (LUL) and left lower lobe (LLL).

Main Fissures. Separate lobes of lung

- **Oblique Fissure**
  - Commence at T4 or T5 & end at anterior CPA on the Right & 5 cm behind from Rt CPA for the Lt.
- **Horizontal Fissure**
  - Extend from hilum to 6th rib at anterior axillary Line
- All fissures seen on Lateral film.
- Horizontal fissure can be visible on a PA film.


Left Oblique Fissure
Horizontal Fissure
Right Oblique Fissure

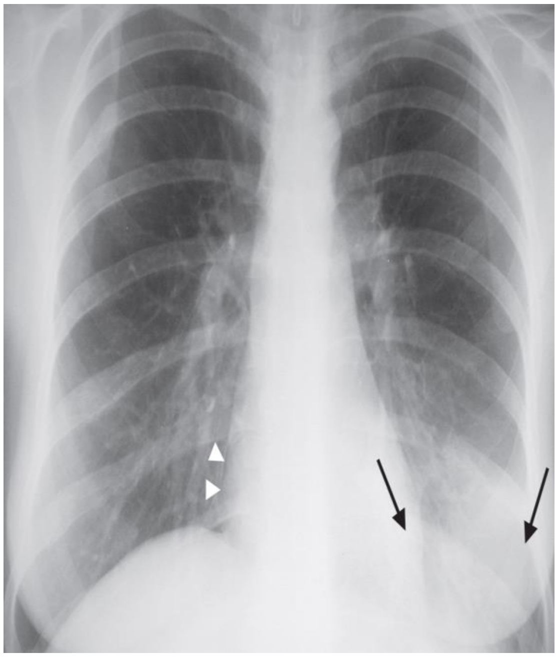
3.8 Lung parenchyma

- Lobar anatomy: Right lung has 3 lobes (upper, middle & lower), Left lung has 2 lobes (upper &lower lobes)
- Causes of **lung lucency**
  - Lung cysts & cavities
  - Emphysema
  - Bronchiectasis
  - Pneumothorax
- Causes of **lung opacity**
  - Consolidation
  - Atelectasis
  - Infiltrations
  - Nodule/ mass
  - Fluid

i. Air space diseases

Consolidation

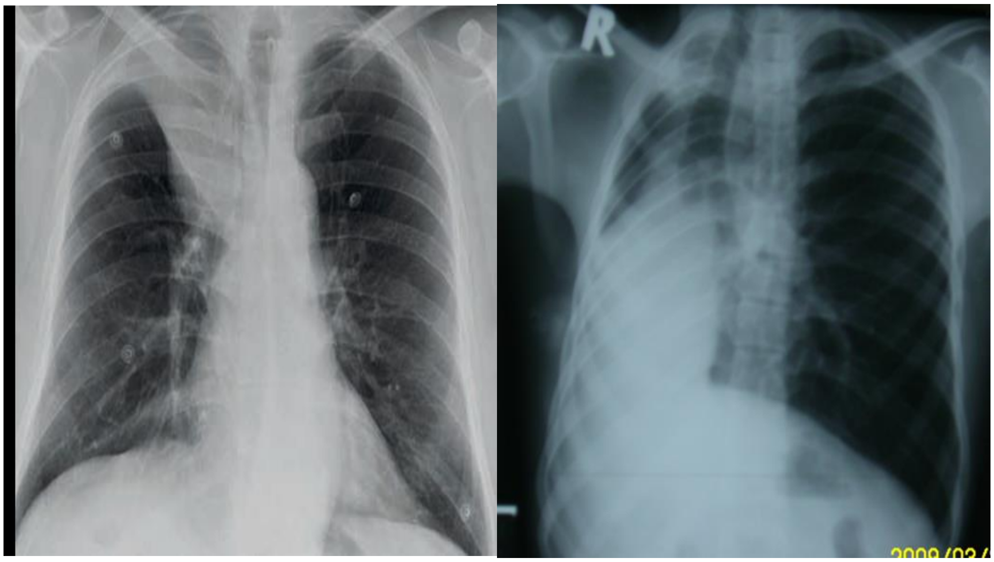
- Filling of alveoli with liquid like substance which causes silhouetting of adjacent structures.
- Common etiologies: Pneumonia, pulmonary hemorrhage, ARDS, pulmonary edema, aspiration, neoplasm
- Air bronchograms: patent air ways filled with air; creating faint luceny with in the consolidated lung. It tells that the opacity is intrapulmonary (not a pleural pathology)



Picture; Silhouette sign: Ill-defined heart border due to consolidation on the para cardiac area. The CXR appearances reflect the loss of air, hence the increase in opacity.

Atelectasis / Collapse:

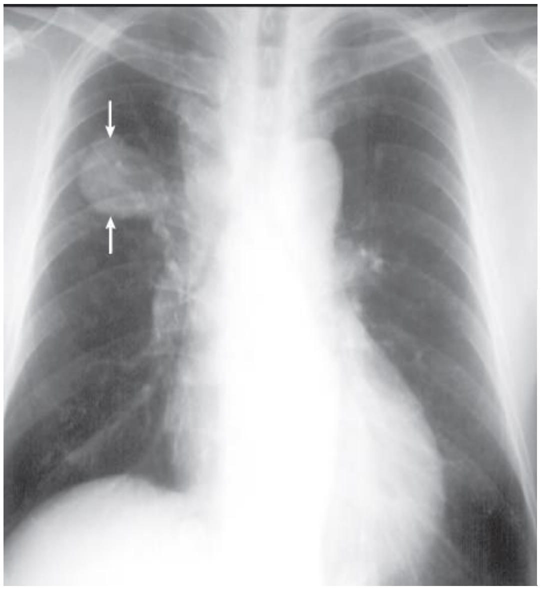
- Loss of lung volume due to decreased aeration.
- Direct signs are from lobar volume loss.
  - Displacement of the fissures & vascular crowding.
- Indirect signs are due to the effect of volume loss on adjacent structures.
  - Elevation of the diaphragm
  - Rib crowding on the side with volume loss
  - Mediastinal shift to the side with volume loss
  - Over inflation of adjacent or contralateral lobes
  - Hilar displacement.



ii. Mass

Interstitial infiltrates:

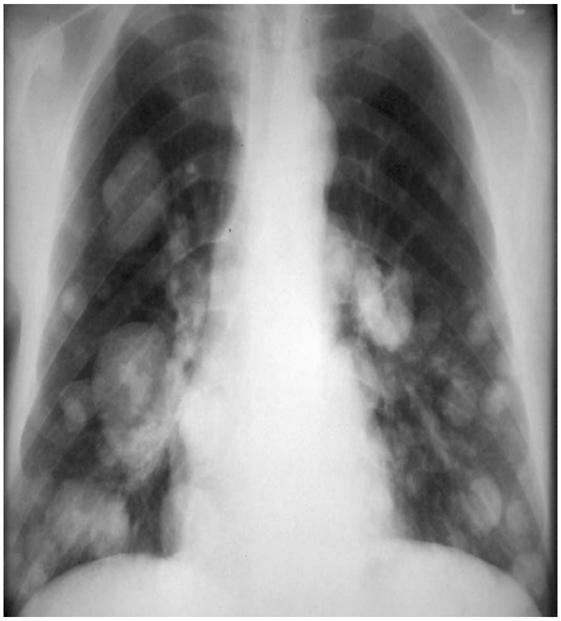
- Nodular
- Reticular/ Reticulonodular
- Milliary: DDx- TB, Hemosiderosis, sarcoidosis, fungal, pneumoconiosis
- Honeycomb pattern



- Nodules and masses are discrete areas of increased lung opacity whose borders do not conform to anatomic divisions (such as a fissure).
- Masses are similar to nodules except that they are larger, measuring greater than 30 mm in diameter.
- Nodules and masses should be described by noting their size, the sharpness of their borders, their number, their location, and the presence or absence of calcification.

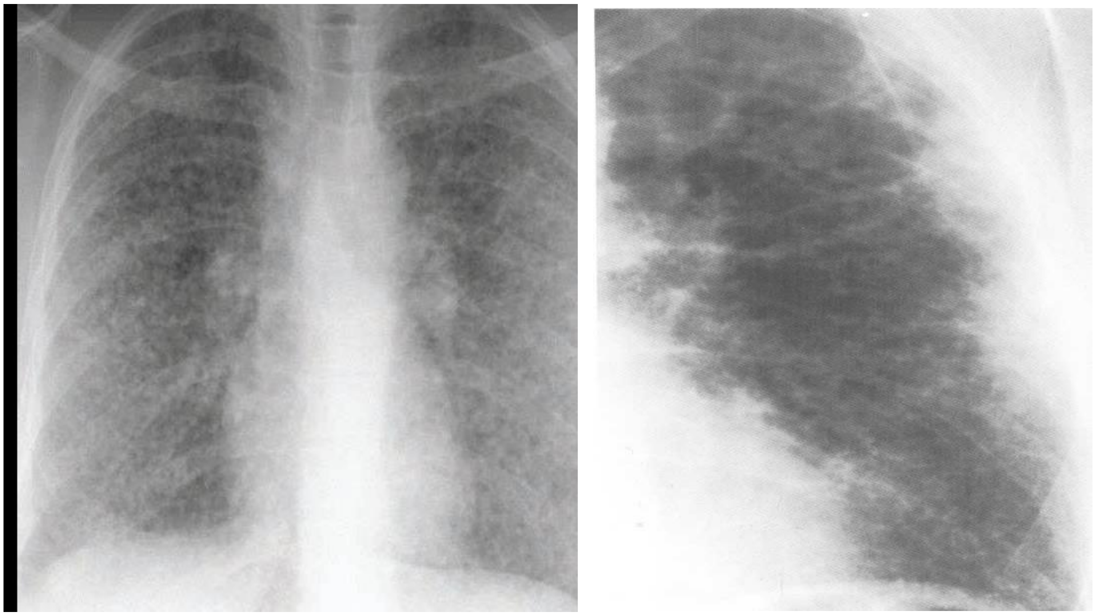
- If the lesion measures less than 3 cm, it is called a nodule. If it is larger than 3 cm, it is called a mass.
- A nodule/mass is caused by either a malignant (e.g. lung cancer, metastasis) or benign process (e.g. hamartoma, granuloma).
- Primary lung cancers tend to have ill-defined, speculated borders, and grow over time. Metastases tend to produce multiple smooth round lung nodules, often of variable size. Benign lesions tend to be small, well defined, smooth, round and maybe calcified. They usually are stable in size when compared to prior films
- A doubling of volume in less than 3 months is unlikely to be a neoplasm but more likely an infective or inflammatory process.
- Doubling times from 3 to 18 months are within the window for malignant lesions

Lung mass



Picture; CXR of an adult male with metastatic renal cell carcinoma. Note the multiple well defined “cannon ball” metastases.

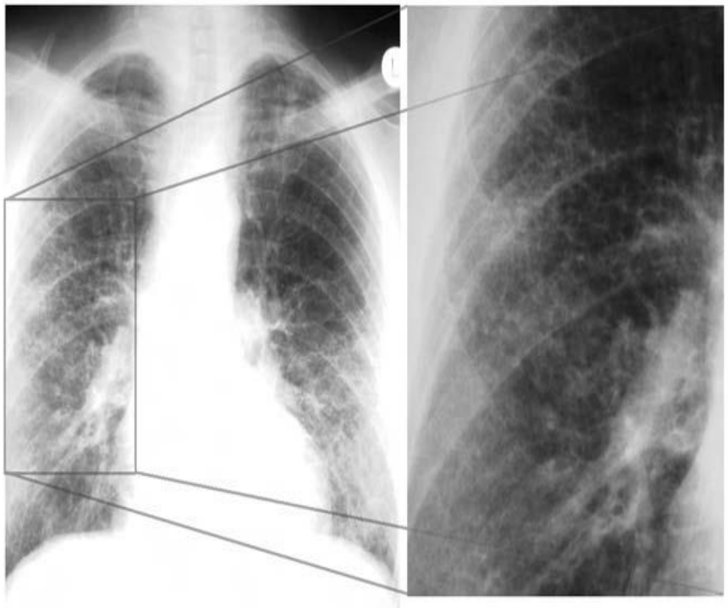
- Lung ca: Tumors < 1 cm in diameter may not be visible on CXR. Cavitation is most likely to be found in SCC (squamous cell carcinoma)



Picture; left) Milliary pattern. Right) Honeycomb pattern representing lung scarring.

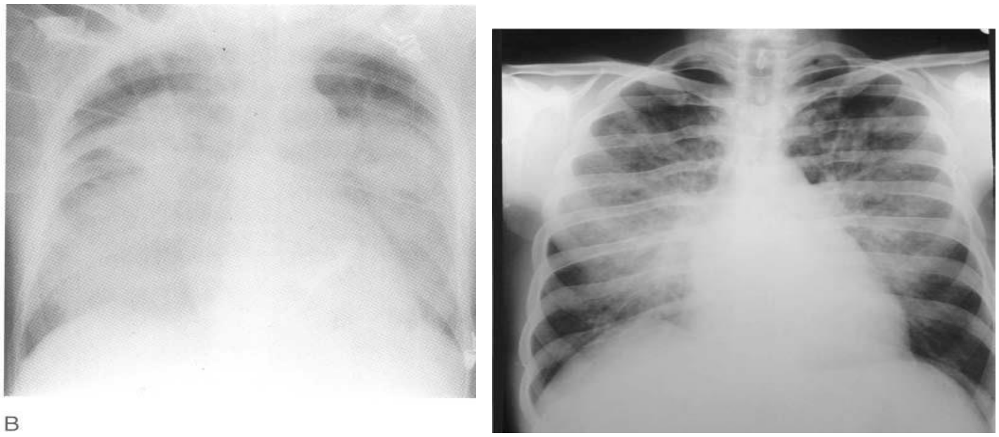
iii. Fibrosis

- The CXR is an insensitive investigation for detecting pulmonary fibrosis.
- HRCT can demonstrate mild to moderate degrees of fibrosis that are not detected on CXR.
- When fibrosis is apparent on CXR the cardinal feature is reticulation, a fine network of lines, corresponding to fibrous thickening of the lung interstitium such that it becomes visible on CXR
- To make a diagnosis of fibrosis the other conditions that thicken the interstitium such as interstitial edema in heart failure, lymphangitis carcinomatosis and alveolar proteinosis, should be excluded or other evidence of fibrosis should be present.
- The presence of volume loss in the region of reticulation and/or honeycomb destruction supports a diagnosis of fibrosis.
- Honeycomb destruction of the lung is primarily a feature of idiopathic pulmonary fibrosis, is characteristically peripheral and basal in site and may be seen on CXR if severe



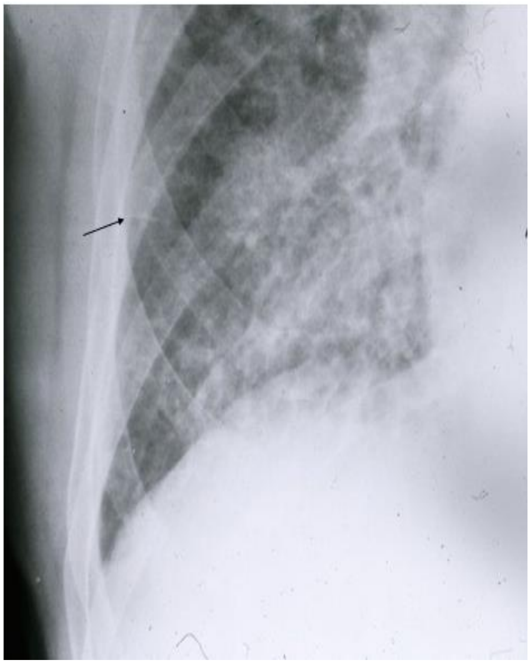
Picture; CXR of a pt with idiopathic pulmonary fibrosis. The magnified area demonstrates the interlacing network of lines/ reticulation, which represent the visible pathologically thickened interstitium, in this case due to fibrosis

iv. Lung opacity: Pulmonary edema



B

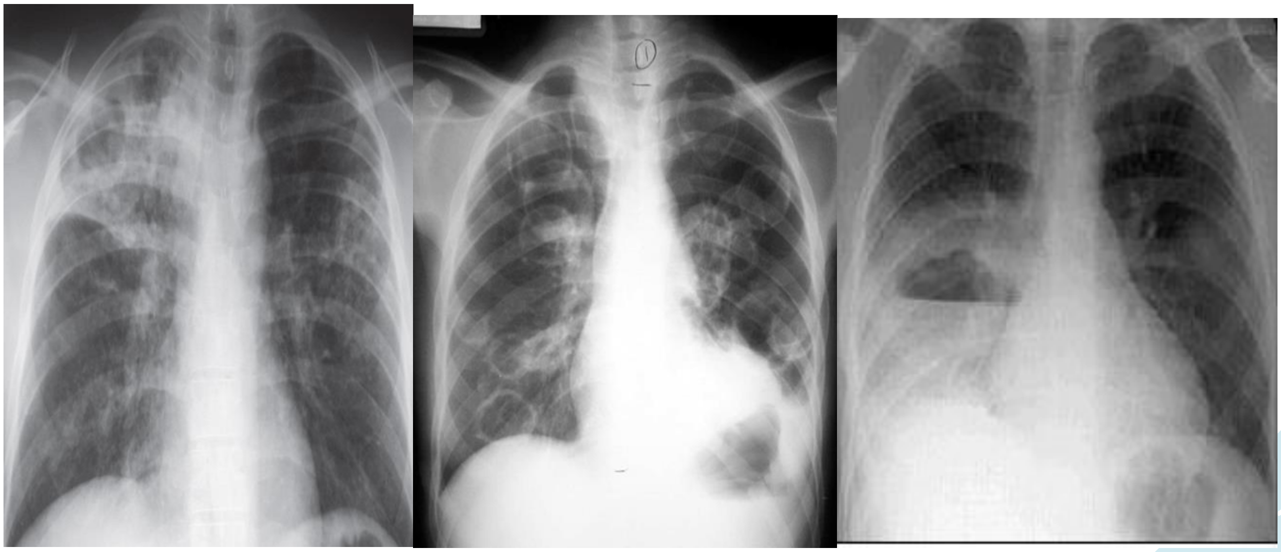
PA CXR: left) typical batwing distribution of air space disease. Right) 1. Vascular redistribution: Cephalization (blood vessels in the upper lung zones become larger than the ones in lower lung zones /the inverse of normal/), 2. Interstitial pattern and Kerly B lines, 3. Peribrochial cuffing (bronchi seen head on are surrounded by fluid Blood diversion), 4. Pleural effusions, 5. Batwing pattern (symmetrical air space disease in the lung adjacent to the hila)



Picture; Kerley B lines (black arrow); Tiny horizontal lines seen at the periphery of the basal lung area, perpendicular to the pleura…represent fluid in the interlobular septa

v. Cavity

- Gas filled space surrounded by complete wall. It has a thick, irregular wall, often with a solid mural component.
- Solitary cavity: most likely infection or primary lung cancer, post traumatic
- Multiple cavitary lesions are typically vascular or spread through the vascular system. DDX are: Aspiration lung abscess, TB, Septic emboli, Vasculitis (Wagner’s granulomatosis), metastases



Pictures; left) Right upper lobe large cavity. Middle) Multiple cavity: Bilateral thin walled cavities…cancer. Right) Lung abscess: air—fluid level

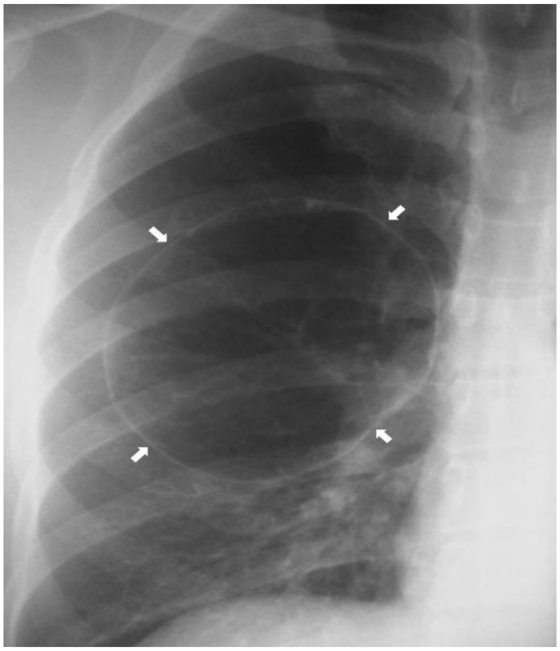
- Cavity location:
    - TB: Upper zone
    - Lung abscess: Right lower zone
    - Amoebic lung abscess: Right basal lung
    - Pulmonary infarction: Basal
- Cavity wall:
    - Thick- neoplasm, acute abscess, wegner's granulomatosis
    - Thin wall- Usually benign e.g. bullae, pneumatocele, hydatid cyst, Chronic inactive TB, traumatic lung cyst
    - Shaggy inner wall — abscess
    - Irregular & nodular — cancer
    - Presence of air fluid level — lung abscess, empyema, TB, cavitating ca
    - Presence of ball inside cavity- Aspergilloma in an old cavity

Note: A cyst may be confused with cavity.

- In general, thin-walled cavities (5 mm) tend to be infective and, when thick-walled (10 mm), SCC of the lung enters into the DDX.
- After a suspected aspiration, chest x-ray abnormalities typically appear within two hours.

vi. Lung cyst

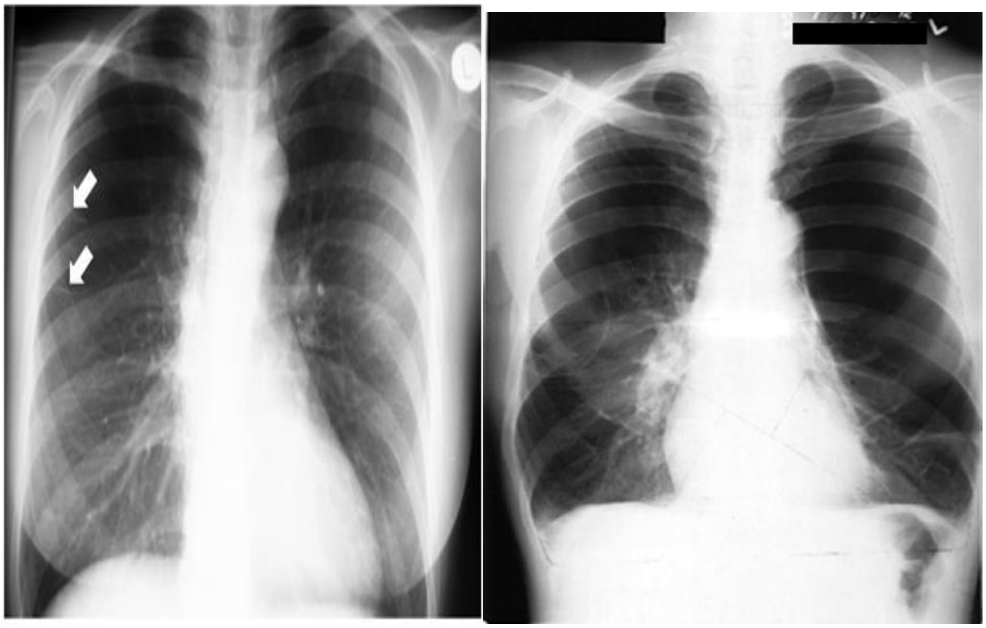
- Cyst is an air-containing lucency with a thin, nearly imperceptible wall. usually due to a primary airway abnormality (e.g. Emphysema, bronchiectasis)
- DDx for a single cyst:
    - Bulla: an air-filled cyst measuring >1 cm
    - Bleb: an air-filled cystic structure contiguous with the pleura measuring <1 cm.
- N.B Rupture of a bleb is commonest cause of spontaneous pneumothorax.
- **Pneumatocele:** is an air-filled space caused by prior lung trauma or as a sequela of pneumonia, typically from A long-term sequel of **S. aureus** or PCP. Pneumatoceles almost always resolve
- The appearance is similar to that of a cavity, but thin walled with no adjacent lung parenchymal opacity to suggest active inflammation



Picture; A pneumatocele in a patient who had a staphylococcal pneumonia as a child. Note the thin wall, the entirety of which is visible (white arrows), unlike the wall of a bulla. NO adjacent parenchymal opacity to suggest active inflammation

vii. Bullous emphysema

- Bullous emphysema is characterized by bullae, which cause areas of absence or paucity of lung markings. Only a proportion of the wall of the bulla is usually visible creating thin curvilinear lines

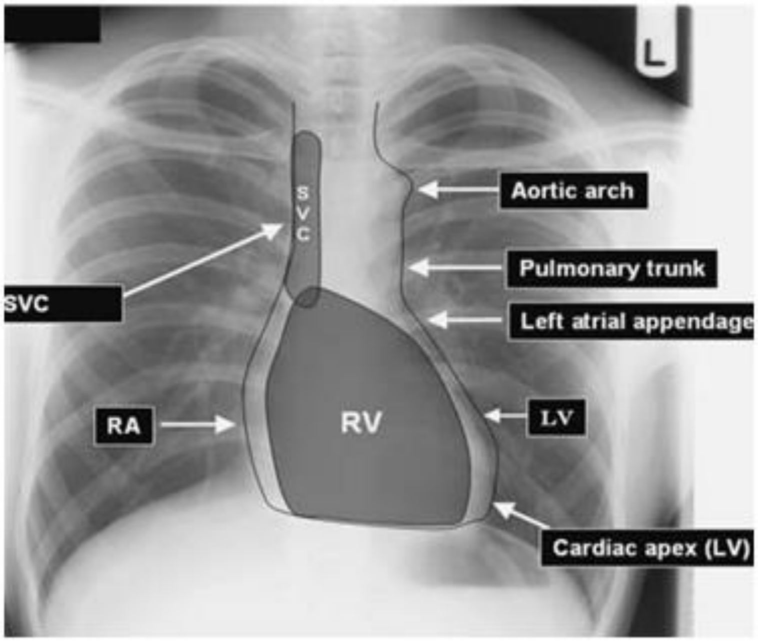


Picture; CXR of a pt with bullous emphysema. Note the curvilinear lines (arrows) formed by the walls of the bullae, but the entire wall is not visible.

3.9. Heart and mediastinum

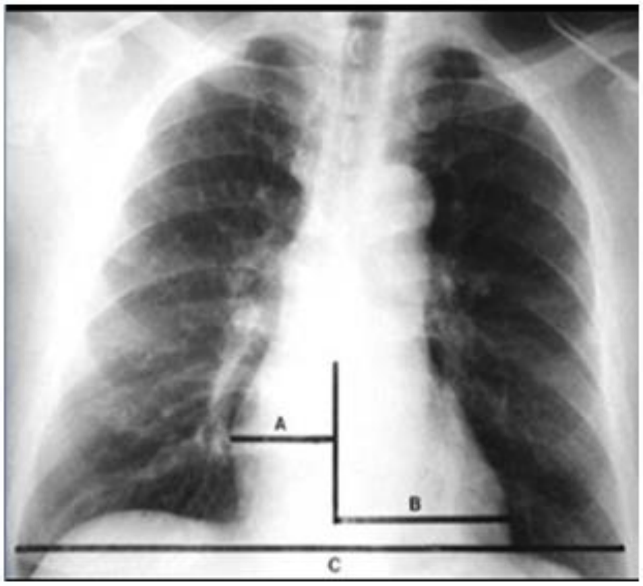
a. Heart

- Central dense shadow
- Cardiac shadow-2/3rd Left side, 1/3rd Right side
- Cardiac silhouette: boundary is (look at picture below)
  - Right border — IVC, RA, SVC
  - Left border — Aortic arch, pulmonary bay, LV, LA appendage



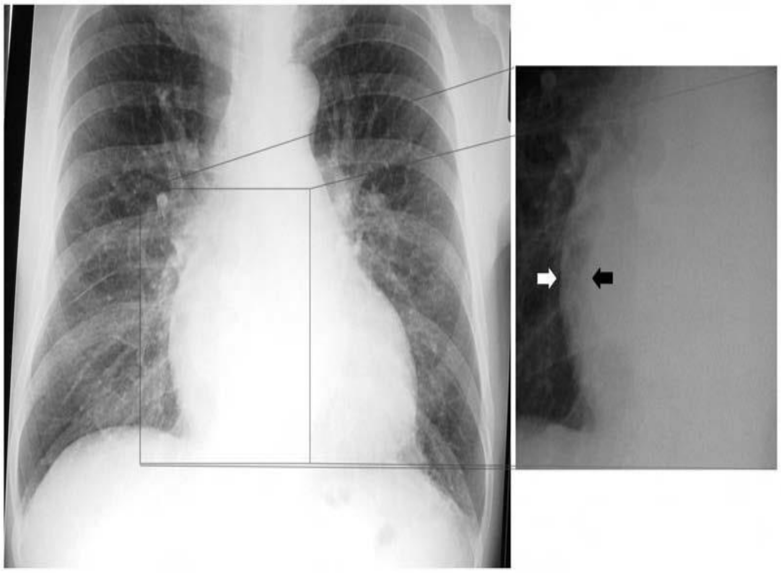
Picture; Cardiac silhouette

- Normal cardiothoracic ratio is 35 - 50 % (look at picture below)
  - Draw a midline (vertical line) along the spinous processes. Take the maximum distance formed by the cardiac silhouette on both sides (A & B on the picture), add them and divide for total thoracic diameter (C on the picture). Multiply by 100%
    - Cardiothoracic ratio = $\frac{\mathbf{A+B}}{\mathbf{C}}\ \mathbf{x\,100}\,\%$ = 35-50%, If > 50 % - cardiomegaly



Picture; cardiothoracic ratio = $\frac{A+B}{C} \times 100\,\%$ = 35-50%, If > 50 % - cardiomegaly

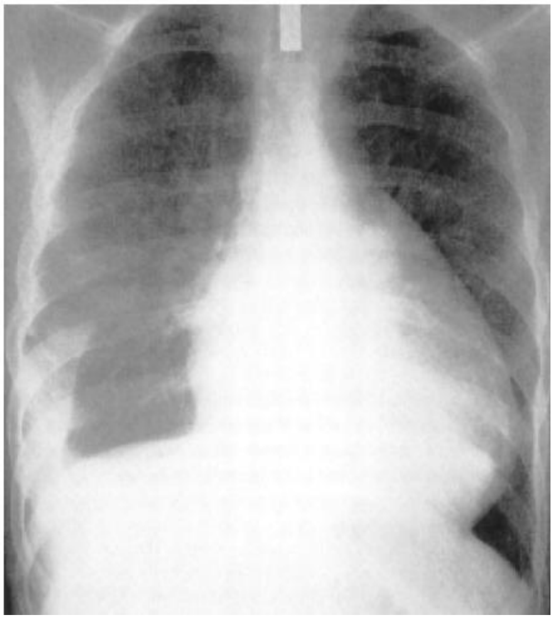
- Heart size will vary with body habitus making absolute lower limits meaningless, but reasonable upper limits for adults are 15.5 cm for females and 16 cm for males.
- Look for evidences of chamber enlargement
  - LA — splaying of carina, straightening of Left heart border, double Right heart border, posterior displacement of esophagus
  - RA — lateral bulging & clear outline of Rt heart border
  - LVH — left & downwards displacement of the apex
  - RVH — Narrowing of the anterior retrosternal clear space on lateral CXR. Round apex with upward and lateral displacement. Obliteration of pulmonary bay b/c of pulmonary artery enlargement
  - LA or RA enlargement & LVH can be seen on P-A CXR; RVH is seen on lateral CXR (causes narrowing of the anterior retrosternal clear space)



Picture: CXR of A pt with early left heart failure. The magnified view demonstrates the double heart border, right atrial wall (white arrow) and left atrial wall (black arrow). Double right heart border: caused by the projection of the right wall of the left atrium behind the silhouette of the right atrium

Pericardial effusion

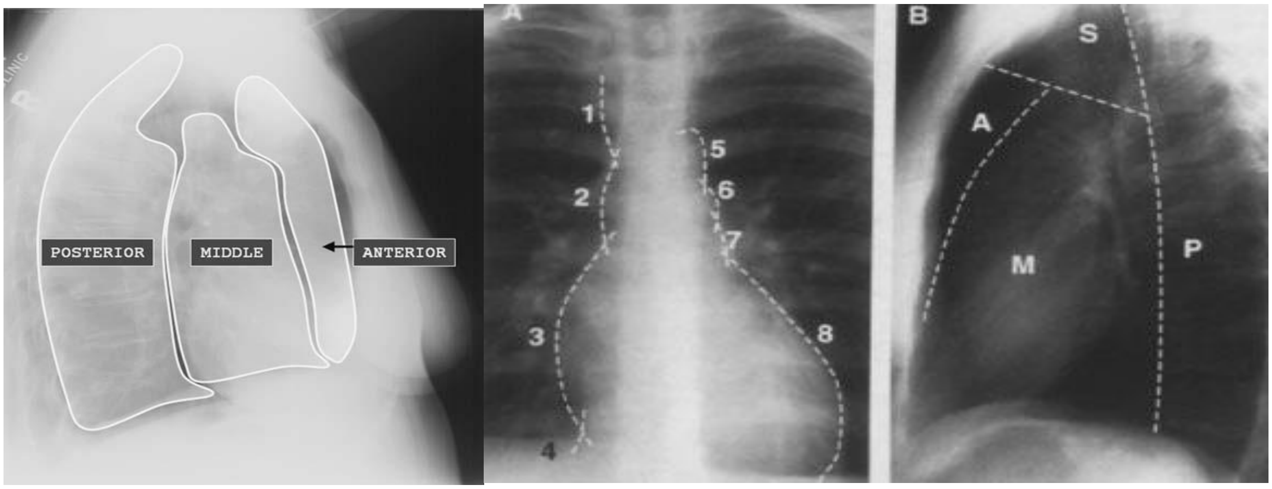
- Pericardial effusions are difficult to appreciate on CXR. The most obvious signs are a change in the shape of the heart to a more rounded contour (the globular heart) and a rapid increase in size of the cardiac silhouette.
- If pericardial fluid is >250 ml, it may be seen on CXR
    - **"Flask shaped" or "water bottle heart"** on erect PA film
    - Globular when supine film
- Pericardial calcifications: appear as curvilinear calcification on the surface of the heart.
- Causes of pericardial calcification
- Pericarditis (TB, rheumatic fever, viruses)
- Post-traumatic



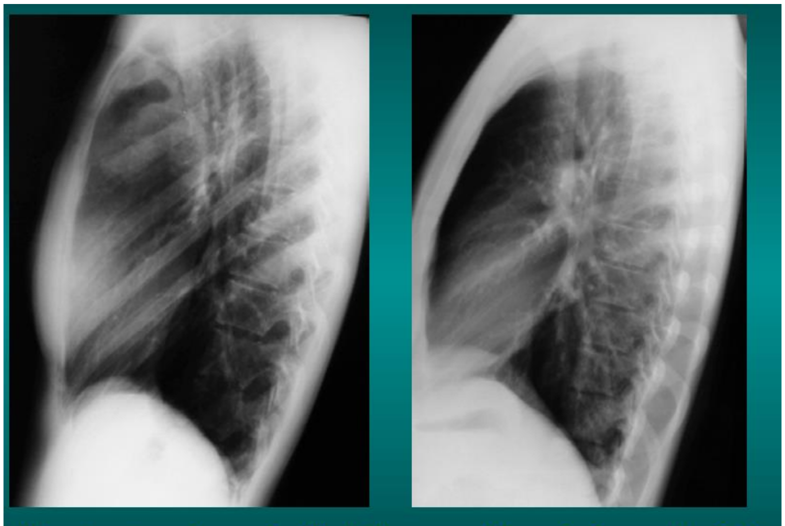
Picture; A water bottle heart

b. Mediastinum:

- Encompasses midline thoracic structures that are delineated by mediastinal pleura, the diaphragm, the sternum, the spine, and the thoracic inlet.
- Divided into Anterior, Middle (visceral) and Posterior (paraspinal) compartments



Picture; Components of the PA mediastinal shadow (A): SVC (1), Ascending aorta (2), RA (3), IVC (4), aortic arch (5), pulmonary trunk (6), LA appendage (7) and, LV (8). Mediastinal compartments on the lateral film (B) include: superior(S), anterior (A), middle (M) and posterior (P) compartments



The retro sternal space is filled: thymoma. Normal view on the right

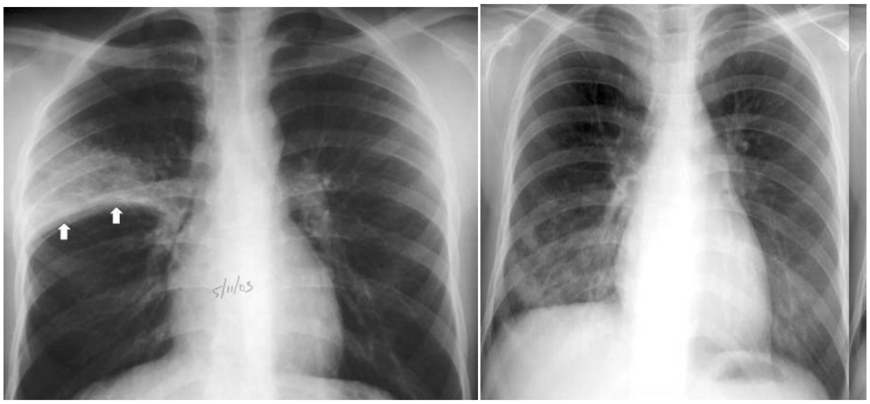
5.4 CXR features of common lung pathologies

Pneumonia

Lobar Pneumonia

- Commences as localized infection of terminal air space
- Uniform consolidation of all or part of a lobe
- Homogenous opacity limited by the fissure
- Normal lung volume

- Air bronchogram seen

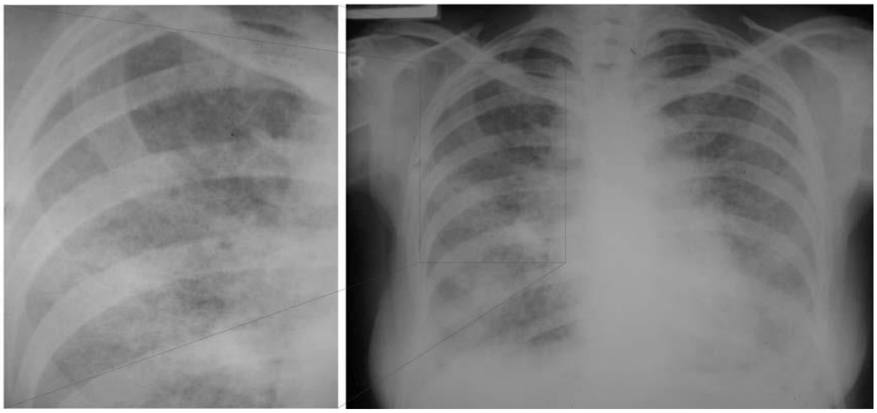


Pictures; Left) Frontal CXR of an adult male with pneumonia confined to the anterior segment of the right upper lobe. Note the inferior demarcation by the minor fissure (white arrows). Right) Atypical pneumonia; Poorly-defined nodular opacities in RLL zone in a pt with Mycoplasma pneumoniae pneumonia.

Broncho Pneumonia

- Causes patchy consolidation
- It Is a multifocal process which commences at terminal & respiratory bronchioles; tend to spread segmentally

Acute hypersensitivity pneumonitis



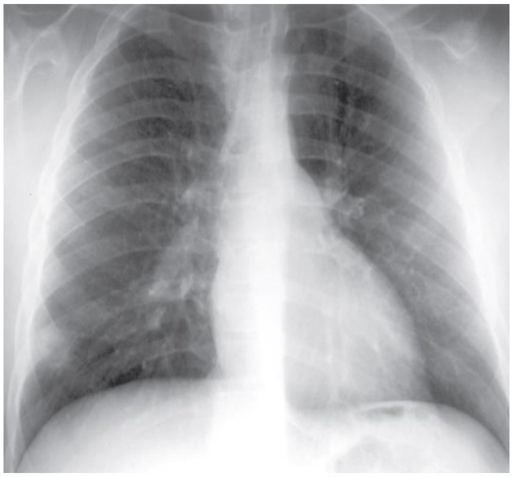
Picture; A frontal CXR of an adult female diagnosed with acute hypersensitivity pneumonitis. Note the **patchy ground grass opacity**.

Pulmonary TB

Primary TB:

- Consolidation, hilar LAP, effusion & milliary disease May occur in any lobe, but most typical locations are the lower lobes or right middle lobe.

- Classic imaging findings are not always seen, but include:
    - Ghon focus: Initial focus of parenchymal infection, usually located in upper part of lower lobe or lower part of upper lobe.
    - Ranke complex: Ghon focus and LAP
- Cavitation is rare

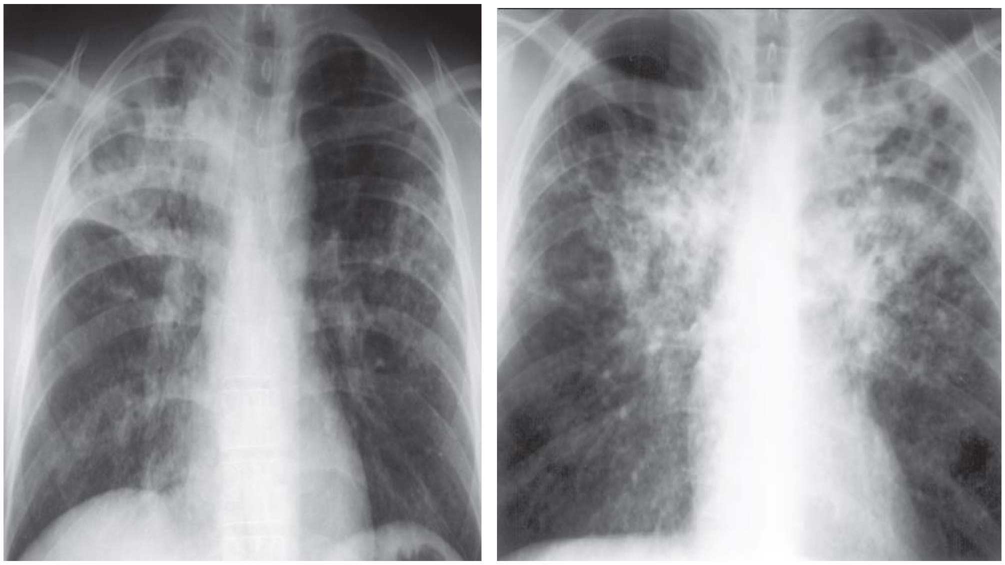


Picture; The Primary complex (Ghon focus & ipsilateral hilar LAP) … Right lower lobe peripheral air space opacity & Right hilar adenopathy

- Because most inspired air is distributed to the middle and lower lung zones, these areas of the lungs are most commonly involved in primary TB

Reactivation TB

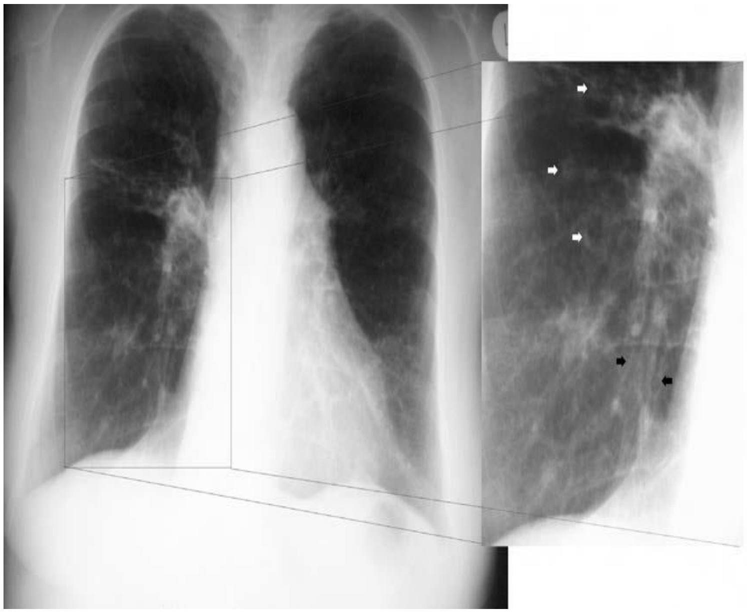
- Upper lobe consolidation with cavity ± fibrosis
- Usually lacks LAP
- May have Pleural effusion/empyema
- It is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth
- **Miliary TB:** It can occur in primary or reactivation TB. diffuse random distribution of tiny nodules seen in hematogenous disseminated TB
- **Healed TB** appears as apical scarring, usually with upper lobe volume loss and superior hilar retraction.
- **Calcified granulomas** may be present as well, which indicate containment of the initial infection by a delayed hypersensitivity response



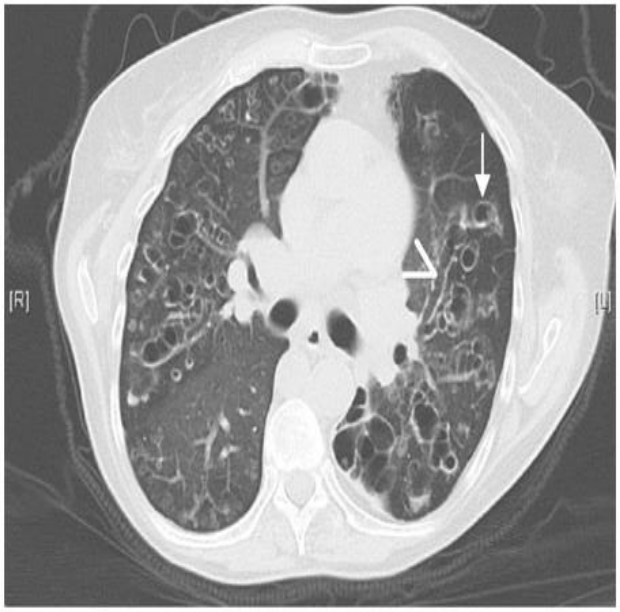
Pictures; left) Right upper lobe large cavity. Right) Upper lobe consolidation with cavitation

Bronchiectasis

- Bronchiectasis is defined by the presence of dilated bronchi with thickened walls.
- CXR is insensitive for the detection of bronchiectasis with only severe disease being identified with any certainty.
- Bronchiectasis is descriptively divided into 3 types; cylindrical, varicose and cystic.
- Chest CT is more specific for bronchiectasis and is the imaging modality of choice for confirming the diagnosis.
- CT findings include airway dilation (detected as parallel "tram tracks" or as the "signet-ring sign"–a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering (including the presence of tubular structures within 1 cm from the pleural surface), bronchial wall thickening in dilated airways, inspissated secretions (e.g., the "tree-in-bud" pattern), or cysts emanating from the bronchial wall (especially pronounced in cystic bronchiectasis



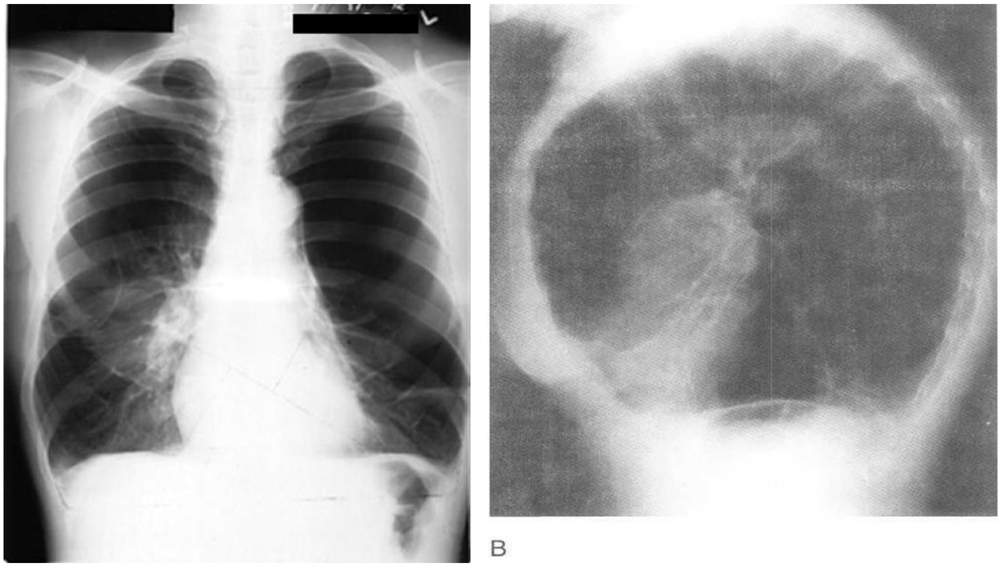
Picture; CXR of a pt with cylindrical bronchiectasis, on the magnified image are ring shadows (white arrows) and **tram tracks or lines** (black arrows), representing dilated bronchi end on and lengthways respectively



Picture; Chest CT; Airway dilation (detected as parallel "tram tracks" or as the "signet-ring sign"–a cross-sectional area of the airway)

COPD

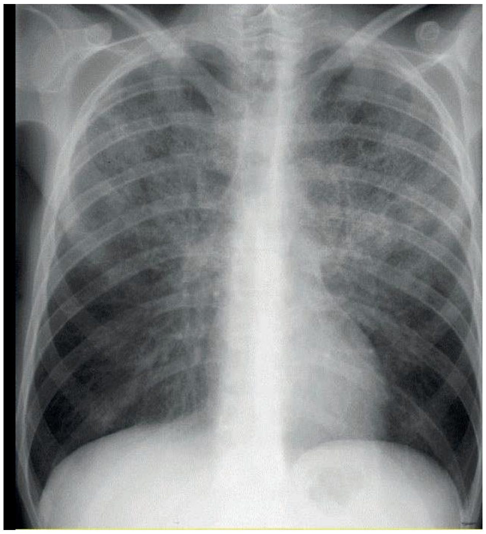
Emphysema



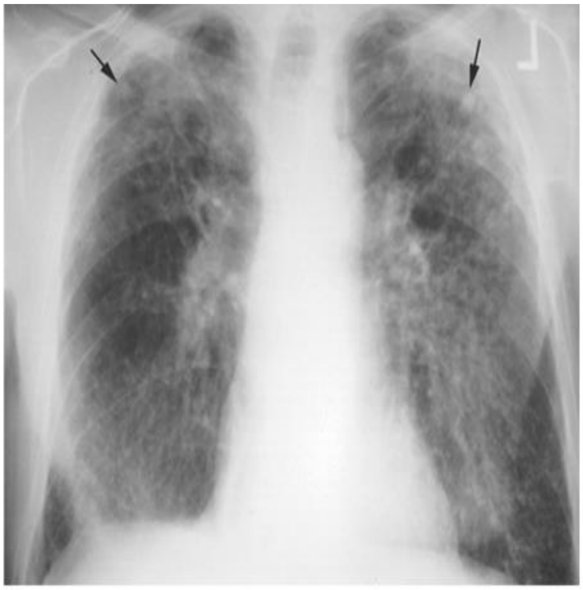
Pictures; A) Hyperlucent, Hyperinflated lungs, Avascular zones. Sometimes, ball-shaped collections of air develop, which are called bullae. On the radiograph, there is an overall decrease in lung density (too black). This makes sense since the fluid density alveolar walls are being destroyed and air is trapped in the lungs. Also, because of tissue destruction, there are fewer visible blood vessels. Ones that are seen sometimes take an abnormal curved course because they are going around destroyed lung. B) Lateral CXR: flattened hemidiaphragms and barrel chest deformity.

PCP

- CXR findings can be normal
- Classic finding is bilateral perihilar (central) airspace opacities with peripheral sparing.
- There is a propensity to cause upper lobe pneumatoceles, which may predispose to pneumothorax or pneumomediastinum.

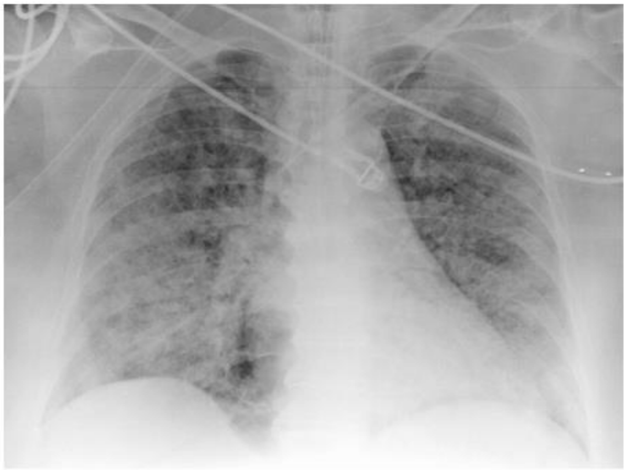


ILD: Silicosis



Picture; A pt with silicosis: variably sized, poorly defined nodules (arrows) predominating in the upper lobes

ARDS



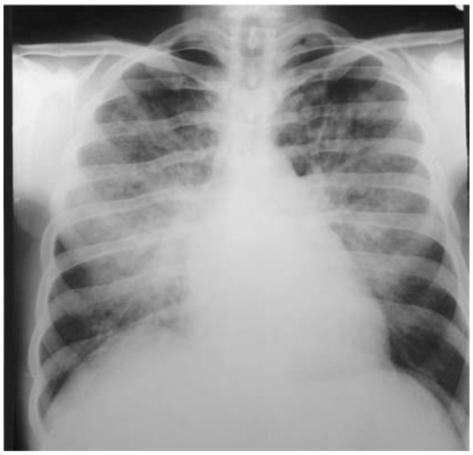
Picture; AP CXR of ARDS that shows diffuse interstitial and alveolar infiltrates, that can be difficult to distinguish from LV failure. BUT the heart size is normal

Pulmonary edema

- Vascular redistribution: **cephalization** of the vessels
- **Interstitial edema**, peri bronchial cuffing, and Kerley B and A lines.
  - Kerley B lines: seen at the peripheral lung; due to thickened interlobular septa.

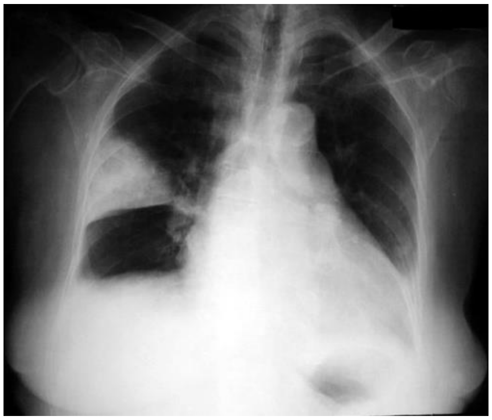
  - Kerley A lines radiate outward from the hila and may represent dilation of lymphatic channels.
- **Alveolar edema**
  - Bilateral perihilar opacifications
  - Bat wing/ butterfly appearance when severe
  - Pleural effusions and cardiomegaly are often present.

Note: pulmonary edema is usually symmetric and dependent



Acute PTE

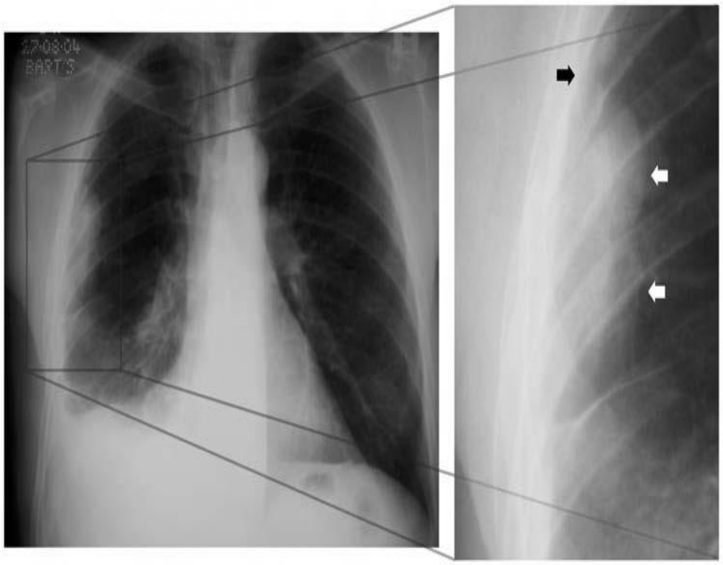
- The CXR is often normal.
- Sometimes a focal, black, **wedge-shaped area** is seen representing infarcted sub-segmental areas of lung that may cavitate, as blood does not fill the blood vessels after the embolism.
  - Focal oligemia (**Westermark's sign**)… Paucity of vascular markings in the region of the PE.
  - A peripheral white wedge-shaped area of air space disease is seen due to post-obstruction infarction (**Hampton's hump**).
- An enlarged right descending pulmonary artery **(Palla's sign**).
- Nonspecific signs include atelectasis and pleural effusion.
- The development of pulmonary arterial hypertension may be evident with prominent proximal pulmonary arteries



Picture; Wedge shaped Pulmonary infarct

Pleural based mass

- If the medial margin is visible, but the lateral margin is indistinct, the mass is probably pleural based



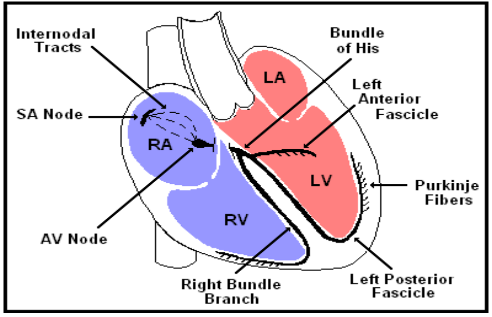
picture; Left image demonstrates a pleural based mass, in this case mesothelioma. Note on the magnified image the well-defined medial margin (white arrows) where the mass is adjacent to the lung and the merging of the upper border with the chest wall (black arrow).

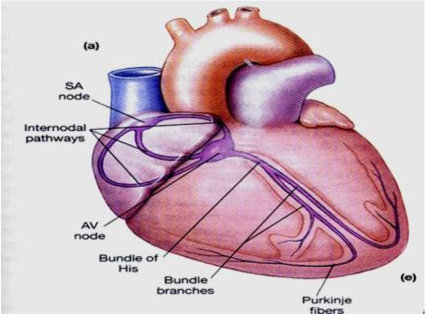
Chapter 6; Basics of ECG and ECG interpretation

Dr. Mulualem. G

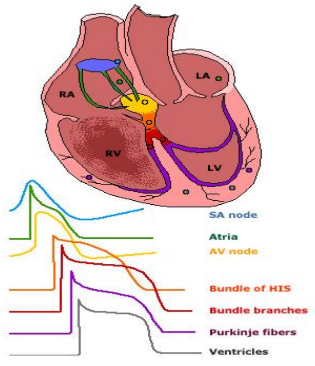
6.1 ECG

- **Electrocardiography** (ECG/EKG) is the process of recording the electrical activity of the heart over a period of time using electrodes placed on the skin through ECG machine.
- The term Electrocardiography is derived from three Greek words. ***Electro*** *= related to electrical activity,* ***Kardio*** *= for heart and* ***graph*** *= to write*
- The graph of voltage v_s time produced by this noninvasive procedure is referred to as **electrocardiogram** (ECG/EKG). That is a surface representation of the electrical events of the cardiac cycle.
- The ECG is the most important test for interpretation of the cardiac rhythm, conduction system abnormalities, and the detection of myocardial ischemia.


Internodal Tracts
Bundle of His
LA
Left Anterior Fascicle
SA Node
RA
LV
Purkinje Fibers
RV
AV Node
Right Bundle Branch
Left Posterior Fascicle


(a)
SA node
Internodal pathways
AV node
Bundle of His
Bundle branches
(e)
Purkinje fibers

Action potentials generated by different parts of conduction system


LA
RA
RV
LV
SA node
Atria
AV node
Bundle of HIS
Bundle branches
Purkinje fibers
Ventricles

Fig; The Normal Conduction System

The sinoatrial (SA) and atrioventricular (AV) nodes generate a slow action potential, mediated by calcium ions. In comparison, the tissues of the atria, ventricles, and the His-Purkinje system generate a fast action potential mediated by sodium ions. Sequential activation of these structures results in the characteristic waveforms visible on the surface electrocardiogram (ECG). The AV node and bundle of His are small structures; as a result, no electrical activity is recorded on the surface ECG during their activation.

Cardiac impulse

- ♥ Cardiac impulse originates in the SA node
- ♥ Traverses the atria simultaneously — no special conduction wires in atria — so **the delay**
- ♥ Reaches AV node — the check post — so **delay**
- ♥ Enters bundle of His and branches — through specialized conducting wires called Purkinje network - activates both ventricles — quick QRS

- First the septum from L to R, then right ventricle and then the left ventricle and finally the apex
- Then the ventricles recover for next impulse

Indication for ECG

- Detection of **MI** and evaluation of other types of **Structural heart disease** including **VHD, CMP, pericarditis, HHD…**
- **Cardiac dysrhythmia**
- **Pulmonary Embolism**
- **Electrolyte abnormalities like hyperkalemia**
- To monitor **drug treatment and toxicity** (specifically antiarrhythmic therapy. e.g. drug induced QT prolongation) and to detect metabolic disturbances.
- Monitoring for **general anesthesia** (pre op, intra op and post op monitoring)
- **Old age with DM or HTN**
- Cardiac stress testing
- Before CTA and MRA of the heart

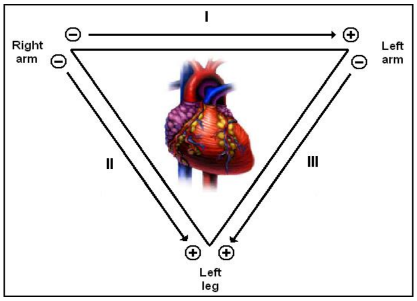
6.2 ECG Leads and electrodes

- **Electrode** is a conductive pad in contact with the body that makes an electrical circuit with the ECG.
  - ✓ On a standard 12-lead ECG there are 10 electrodes (RA, LA, RL, LL, V1-V6)
- **A lead** is usually more abstract and is the source of measurement of vector.
  - ✓ 12 lead ECG has 3 sets of leads
    - a. 3 standard limb leads (I, II, III)
    - b. 3 augmented limb leads (aVR, aVF, aVL),
    - c. 6 precordial (chest) leads (V1- V6)
  - ✓ Cardiac Monitors→ usually limb leads
- In clinical practice the term lead and electrode are used interchangeably, although this is not technically correct.

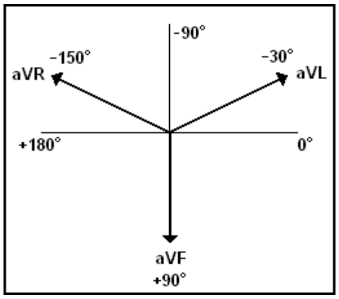
(aVR = lead augmented vector right, aVL = lead augmented vector left, aVF = lead augmented vector foot, RA = right arm, LA = left arm, RL = right leg, LL = left leg, V1-V6 = vector 1 — vector 6)

ECG leads — Standard and augmented leads

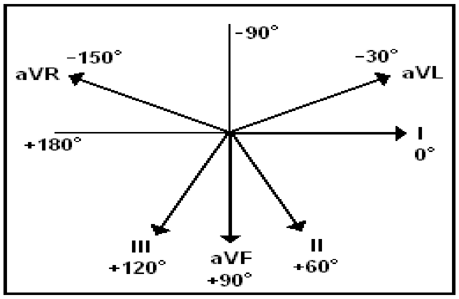
- I -potential difference between Left hand electrode and right-hand electrode (lateral LV)
- II- potential difference between Left foot electrode and right-hand electrode (inferior LV)
- III- potential difference between Left hand electrode and left foot electrode (inferior LV)
- aVR- Right hand electrode and center of heart
- aVL- Left hand electrode and center of heart(lateral)
- aVF- Left foot electrode and center of heart(inferior)


I
Right arm
Left arm
⊖
⊕
II
III
Left leg

Standard Limb Leads

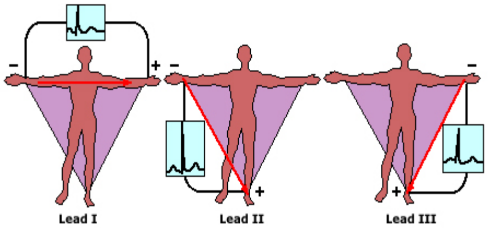

-90°
-150°
aVR
-30°
aVL
+180°
0°
aVF
+90°

Augmented Limb Leads


-90°
-150°
aVR
-30°
aVL
+180°
I
0°
III
+120°
aVF
+90°
II
+60°

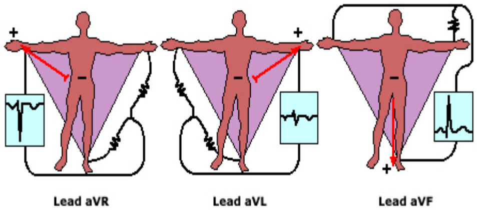
All Limb Leads

Bipolar limb lead system


-
+
Lead I
Lead II
Lead III

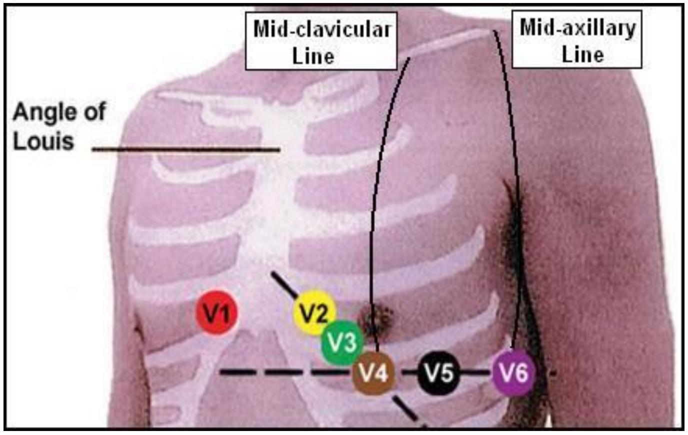
Einthoven described a system of three bipolar leads located at the right arm, left arm, and left leg to form a triangle. Lead I represents the potential difference between the right and left arm; an electrical impulse moving from right to left generates a positive ECG deflection in this lead. Lead II is the potential difference between the right arm and leg; a positive ECG deflection occurs when the impulse direction is toward the leg. Lead III is the potential difference between the left arm and leg; there is a positive ECG deflection when the impulse direction is toward the leg.

Augmented limb leads


+
-
Lead aVR
Lead aVL
Lead aVF

The potential difference between the reference electrode and an exploring electrode constitutes the augmented lead. The three exploring electrodes are the right arm (R), the left arm (L), and the left leg (F). The electrical signals for the unipolar leads are "augmented" by disconnecting the exploring electrode from the reference electrode. Since the reference electrode has zero potential, the augmented potential represents only that measured by the three electrodes. The three augmented leads are designated aVR, aVL, and aVF. An impulse directed toward a limb lead records a positive or upright deflection in that lead.

Placement of precordial leads over the chest


Mid-clavicular Line
Mid-axillary Line
Angle of Louis
V1
V2
V3
V4
V5
V6

Fig; Precordial Leads

1. V1 *(Red)* → at 4th Right ICS, just right to the sternum
2. V2 (*Yellow)* → at 4th left ICS, just left to the sternum
3. V3 *(Green)* → Midway Between V2 and V4
4. V4 *(Brown)* → at 5th left ICS, along the MCL *(place V4 before placing v3 to the chest wall)*
5. **V5** ***(black)*** → at 5th left ICS, along the AAL or halfway between V4 and V6 if the anterior axillary line is unclear.

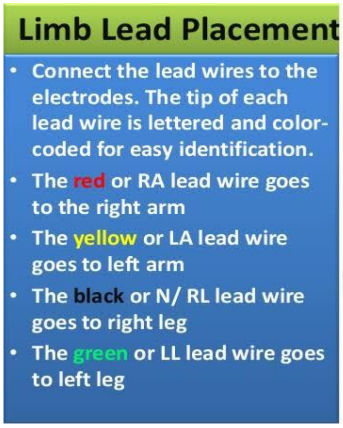
6. V6 *(violet)* → at 5th left ICS, along the MAL

Placement of Limb leads

- Limb lead electrodes are placed on the arms and legs distal to the shoulders and hips.
    1. RL ***(black)*** → On the right leg, Avoid thick muscles
    2. LL *(Green)* → On the left leg, in the same location where RL is placed
    3. LA *(Yellow)* → On the left arm
    4. RA *(Red)* → On the right arm in the same location where LA is placed

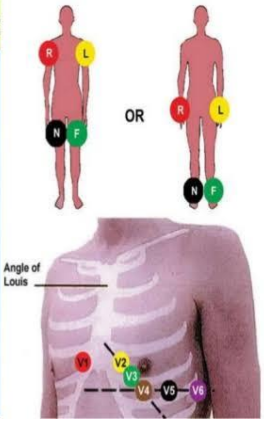
Tip → recognize the colors for fast placement

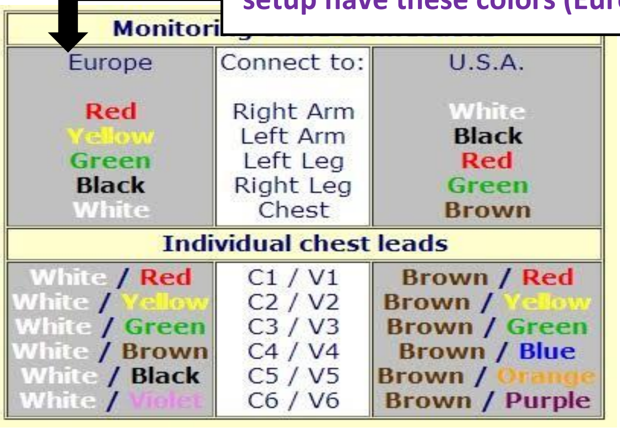
Majority of ECG machines available in our setup have these colors (Europe form)



Limb Lead Placement

- Connect the lead wires to the electrodes. The tip of each lead wire is lettered and color-coded for easy identification.
- The red or RA lead wire goes to the right arm
- The yellow or LA lead wire goes to left arm
- The black or N/ RL lead wire goes to right leg
- The green or LL lead wire goes to left leg





Monitori

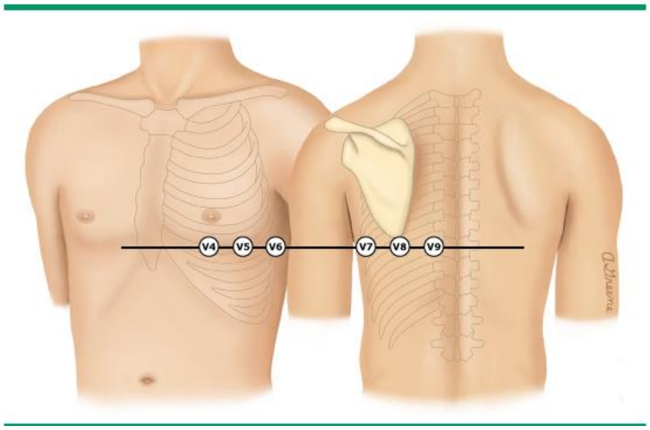
Europe	Connect to:	U.S.A.
Red	Right Arm	White
Yellow	Left Arm	Black
Green	Left Leg	Red
Black	Right Leg	Green
White	Chest	Brown
Individual chest leads		
White / Red	C1 / V1	Brown / Red
White / Yellow	C2 / V2	Brown / Yellow
White / Green	C3 / V3	Brown / Green
White / Brown	C4 / V4	Brown / Blue
White / Black	C5 / V5	Brown / Orange
White / Violet	C6 / V6	Brown / Purple

Summary of Leads

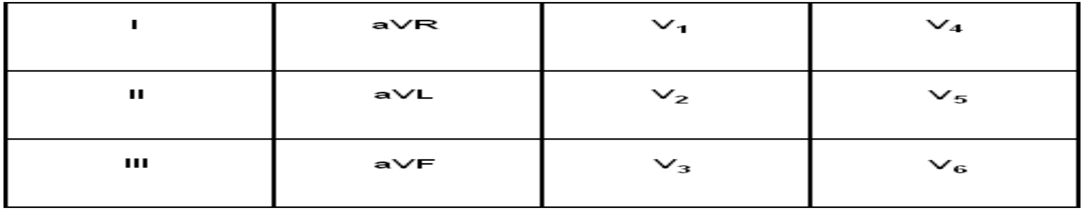
	Limb Leads	Precordial Leads
Bipolar	I, II, III (standard limb leads)	
Unipolar	aVR, aVL, aVF (augmented limb leads)	V_1-V_6
Category of leads		
Category	**Leads**	**Activity**
Inferior leads	II, III, aVF	Look at electrical activity from the inferior (diaphragmatic) surface of heart. E.g. inferior MI
Lateral leads	I, aVL, aVR, V5, V6	Look at electrical activity from the lateral wall of LV. E.g. LVH

Septal leads	V1, V2	Look at electrical activity from the septal surface of heart /interventricular septum/. E.g. septal wall hypertrophy
Anterior leads	V3, V4	Look at electrical activity from the anterior wall of RV and LV (sternocostal surface of the heart). E.g anterior MI
Posterior leads	V7, V8, V9	Acute posterior wall MI induces ST elevations in leads placed over the back of the heart

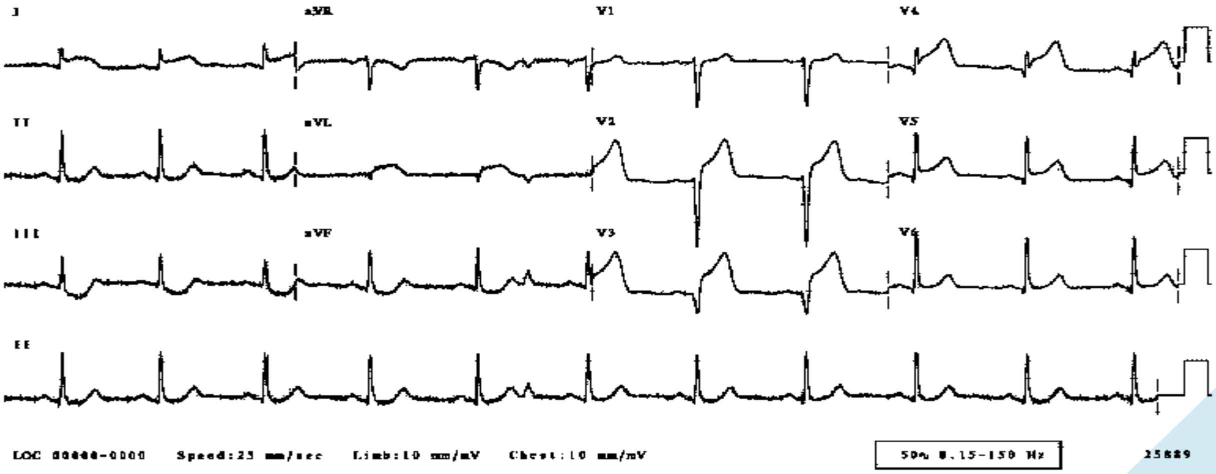
Posterior leads V7 to V9


V4
V5
V6
V7
V8
V9

Arrangement of Leads on the ECG Paper



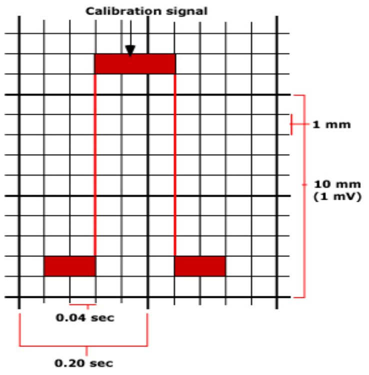
I	aVR	V_1	V_4
II	aVL	V_2	V_5
III	aVF	V_3	V_6


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
LOC 00000-0000 Speed:25 mm/sec Limb:10 mm/mV Chest:10 mm/mV
50~ 0.15-150 Hz
25889

6.3 ECG GRID

- ECG is a plot of **voltage on the vertical axis against time on the horizontal axis.**
- The ECG waves are recorded on special graph paper that is divided into 1 mm^2 grid-like boxes (figure 1).
- The ECG paper speed is ordinarily 25 mm/sec. As a result, each 1 mm (small) horizontal box corresponds to 0.04 second (40 ms), with heavier lines forming larger boxes that include five small boxes and hence represent 0.20 sec (200 ms) intervals.
- On occasion, the paper speed is increased to 50 mm/sec to better define waveforms. In this situation, there are only six leads per sheet of paper. Each large box is therefore only 0.10 sec and each small box is only 0.02 sec. In addition, the heart rate appears to be one-half of what is recorded at 25 mm/sec paper speed, and all of the ECG intervals are twice as long as normal. Other paper speeds are occasionally used.
- **Vertically, the ECG graph measures the height (amplitude)** of a given wave or deflection, as 10 mm (10 small boxes) equals 1 mV with standard calibration.
- On occasion, particularly when the waveforms are small, double standard is used (20 mm equals 1 mv).
- When the wave forms are very large, half standard may be used (5 mm equals 1 mv).
- Paper speed and voltage are usually printed on the bottom of the ECG.

Grid lines and standardization of the ECG



The electrocardiogam is recorded on paper that has large boxes (heavy lines) of 0.5 cm sides. On the horizontal axis, each large box, which represents 0.2 seconds at a typical paper speed of 25mm/sec, is divided into five smaller boxes, each one representing 0.04 seconds. On the vertical axis, the large box also has five subdivisions, each 1 mm in height; 10 mm equals 1 mV with standard calibration.

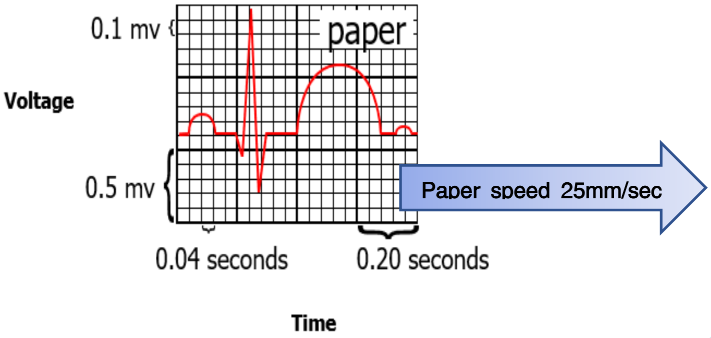
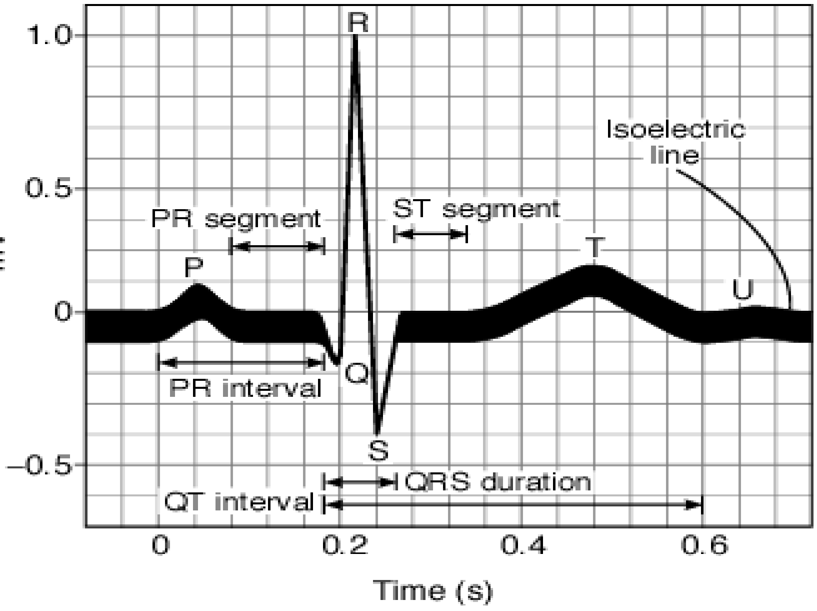
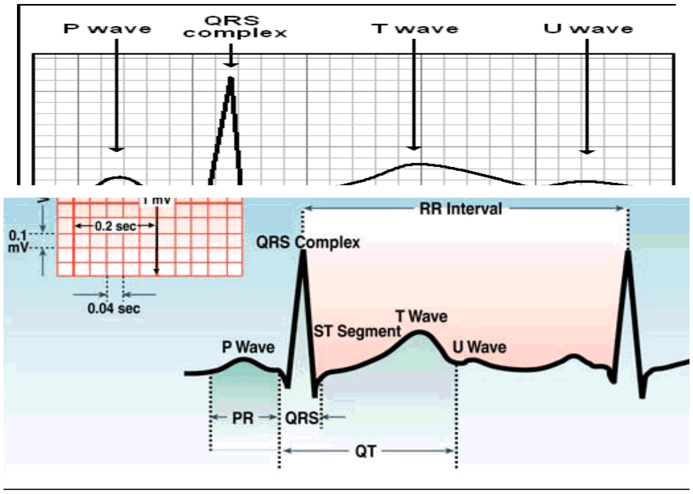


figure 1

Summary
- X-Axis represents time - Scale; X-Axis → 1 mm = 0.04 sec
- Y-Axis represents voltage - Scale; Y-Axis → 1 mm = 0.1 mV
- One big square on X-Axis = 0.2 sec (big box)
- Two big squares on Y-Axis = 1 milli volt (mV)
- Each small square is 0.04 sec (1 mm in size)
- Each big square on the ECG represents 5 small squares = 0.04 x 5 = 0.2 seconds
- 5 such big squares = 0.2 x 5 = 1sec = 25 mm
- One second is 25 mm or 5 big squares
- One minute is 5 x 60 = 300 big squares

6.4 ECG COMPLEXES AND INTERVALS


1.0
0.5
0
−0.5
R
Isoelectric line
PR segment
ST segment
T
P
U
Q
PR interval
S
QT interval
QRS duration
0
0.2
0.4
0.6
Time (s)

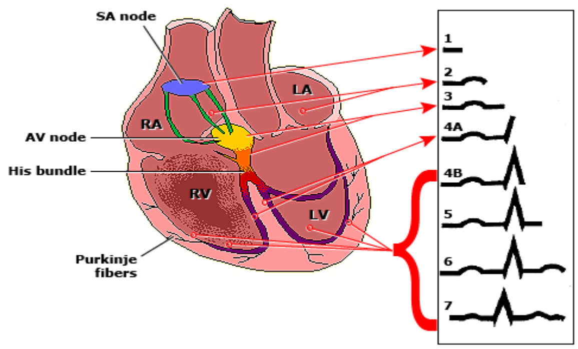

P wave
QRS complex
T wave
U wave
1 mv
0.1 mV
0.2 sec
0.04 sec
RR Interval
QRS Complex
T Wave
ST Segment
P Wave
U Wave
PR
QRS
QT

Table; ECG Complex

Wave or Interval	Description	Duration	Amplitude	Some abnormality examples
P wave	♥ The sequential activation of the right and left atrium (atrial depolarization).	♥ <0.12 sec (3 small boxes)	♥ <0.25 mv (2.5 small boxes)	♥ Picked - >3mm shows right atria enlargement ♥ Wide and bifid : > 0.12 sec and bifid shows left atrial enlargement
QRS complex	♥ QRS complex shows Right and left ventricular depolarization	♥ Normal duration of QRS complex is 0.06 to 0.10 seconds (1½ to 2½ small boxes). ♥ Doesn't affected by heart rate	♥	♥
	Q wave ♥ Septal depolarization	♥ < 0.04 sec (1 small box)	♥ < 3 mm (<3 small boxes)	♥
	R wave ♥ Ventricular contraction	♥	♥ < 15 mm (<15 small boxes)	♥
	S wave ♥ Complimentary to R	♥	♥	♥
ST segment	♥ Electrical silence ♥ Measured from the end of QRS complex to the beginning of T wave on the isoelectric line	♥ Isoelectric	♥ A normal ST segment is flat along the isoelectric line	♥ ST segment elevation greater than 2mm above the baseline or depression of greater than 1 mm below the baseline may be indicative of MI.

T wave	♥ Ventricular repolarization ♥ Friend of ST	♥ 0.08 to 0.12 sec (2-3 small boxes)	♥	♥ Tall peaked T waves indicate hyperkalemia. ♥ Inverted T waves are suggestive of myocardial ischemia or a ventricular conduction delay. ♥ T waves that are larger or smaller than normal may indicate and electrolyte imbalance.
U wave	♥ A small rounded positive gradual or abrupt slope after the T wave and occurs before the P wave. ♥ Not usually present on an ECG unless the heart rate is slow. ♥ Represents Purkinge fiber repolarization	♥	♥	♥ Prominent U waves may be drug related or indicate hypokalemia
TP segment	♥ Ventricular relaxation	♥ shortened in tachycardia	♥	♥
PR interval	♥ Time interval from onset of atrial depolarization to onset of ventricular depolarization. ♥ It is measured from the beginning of the P wave to the first part of the QRS complex (which may be a Q wave or R wave).	♥ 0.12 to 0.20 sec (3-5 small boxes). ♥ The length of the PR interval changes with heart rate.	♥	♥ Prolonged P-R interval in ARF
QT INTERVAL	♥ Duration of ventricular depolarization and repolarization ♥ Measured from the beginning of the Q wave to the end of the T wave on the isoelectric line	♥ 0.36-0.44 seconds (<10 small boxes or 2 large squares)	♥	♥ A prolonged QT interval may indicate prolonged ventricular repolarization and relative refractory period. It can be caused by some of the **cardiac drugs, hypocalcemia, MI, Myocarditis or pericarditis, and LVH.** ♥ A shortened QT may indicate hypercalcemia or be seen in patients taking digitalis.
RR interval	♥ Duration of ventricular cardiac cycle ♥ Used to check rhythm of cardiac cycle	♥ 0.80 sec (20 small boxes or 4 large squares)	♥	♥

Formation of the major deflections on the ECG



1. SA node discharge no deflection
2. Right and left atrial activation: P wave
3. Activation of AV node and bundle of His: No deflection
4A. Septal activation: Onset of QRS complex, initial septal Q wave
4B. Left ventricular free wall activation: Inscription of QRS complex
5. Full ventricular activation: No deflection
6. Ventricular repolarization: His Purkinje T wave
7. Late ventricular repolarization: His Purkinje U wave

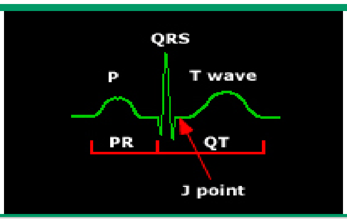
Figure; Formation of the major deflections on the ECG

The electrical impulse is initiated in the sinus node and then activates the right and left atria, generating the P wave. Impulse conduction through the atrioventricular (AV) node and bundle of His, which are small structures, does not generate any ECG activity; this period of "electrical silence" is the PR interval. The first part of the ventricle to be depolarized is the left side of the interventricular septum, producing a small septal Q wave, followed by depolarization of the remainder of the ventricular myocardium, generating the full QRS complex. The T wave represents ventricular repolarization. A U wave may be present, representing repolarization of the His Purkinje system.

❖ ECG is composed of several different waveforms that represent electrical events during each cardiac cycle in various parts of the heart (figure 2).

- ❖ ECG waves are labeled alphabetically starting with the P wave, followed by the QRS complex and the ST-T-U complex (ST segment, T wave, and U wave).
- ❖ The J point is the junction between the end of the QRS and the beginning of the ST segment (waveform 1).

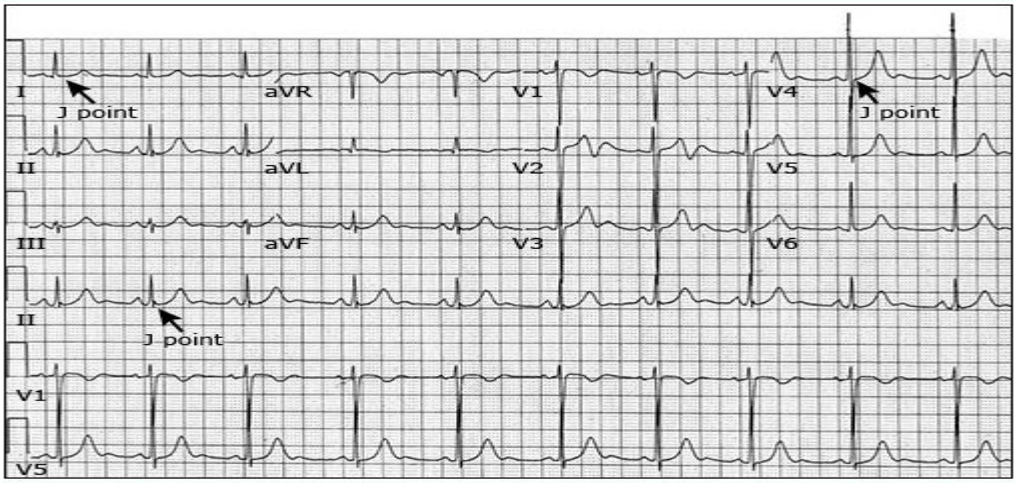
ECG complexes and intervals



ECG waves are labeled alphabetically starting with the P wave, followed by the QRS complex, and the ST-T complex (ST segment and T wave). The J point is the junction between the end of the QRS and the beginning of the ST segment. The PR interval is measured from the beginning of the P wave to the first part of the QRS complex. The QT interval consists of the QRS complex which represents only a brief part of the interval, and the ST segment and T wave which are of longer duration.

Figure 2

J point



The J point is the junction between the end of the QRS and the beginning of the ST segment.

(waveform 1)

A. P wave

- The P wave represents atrial depolarization.
- The normal sinus P wave demonstrates depolarization from the right to left atrium and is an initial low amplitude deflection preceding the QRS complex that is positive in most leads.
- **The duration is generally <0.12 sec (3 small boxes) and the amplitude <0.25 mv (2.5 small boxes).**
- Since right atrial depolarization precedes that of the left atrium (as the sinus node is in the high right atrium), the P wave is often notched in the limb leads and usually biphasic in lead V1.

- The initial positive deflection in V1 is due to right atrial depolarization that is directed anteriorly, while the second negative deflection represents left atrial depolarization that is directed posteriorly.
- The atrial repolarization sequence (atrial ST and T wave phases) occurs just before, simultaneously, and just after depolarization of the ventricular myocardium.
- The atrial "T wave" itself is usually hidden by the QRS complex and not observed on the routine ECG.
- In addition, the amplitude of the atrial T wave is often too small to be observed at standard gain.
- Clinically, atrial repolarization (the atrial ST phase) is most evident during acute pericarditis, in which one often sees PR segment elevation in lead aVR and PR segment depression in the infero-lateral leads, reflecting an atrial current of injury.
- The low amplitude atrial T wave may also be unmasked in certain cases of high degree AV block, especially when the atria are enlarged.
- Finally, alterations in the atrial ST segment and T wave may occur with other pathologies, such as atrial infarction or atrial tumor invasion.

B. QRS complex

- ✓ The QRS complex represents the time for ventricular depolarization.
- ✓ **The entire QRS duration normally lasts for 0.06 to 0.10 seconds (1½ to 2½ small boxes) and is not influenced by heart rate.**
- ✓ If the **initial deflection is negative**, it is termed a **Q wave**.
- ✓ Small Q waves are often seen in leads I, aVL, and V4-V6 as a result of initial septal depolarization and are considered normal.
- ✓ The **first positive deflection of the QRS complex is called the R wave.** It represents **depolarization of the left ventricular** myocardium.
- ✓ Right ventricular depolarization is obscured because the left ventricular myocardial mass is much greater than that of the right ventricle.
- ✓ The small R wave in lead V1 represents initial septal depolarization.
- ✓ The **negative deflection following the R wave is the S wave**, which represents **terminal depolarization of the high lateral wall.**
- ✓ If there is a second positive deflection, it is known as an R'.
- ✓ Lower case letters (q, r, or s) are used for relatively small amplitude waves of less than 0.5 mV (less than 5 mm with standard calibration).
- ✓ An entirely negative QRS complex is called a QS wave.
- ✓ The R wave should progress in size across the precordial leads V1-V6.
- ✓ Normally there is a small R wave in lead V1 with a deep S wave.
- ✓ The R wave amplitude should increase in size until V4-V6 while the S wave becomes less deep. This is termed R wave progression across the precordium.

C. ST segment

- ❖ The ST segment **occurs after ventricular depolarization has ended and before repolarization has begun.**
- ❖ It is a time of electrocardiographic silence.
- ❖ The intersection of the end of the QRS complex and the initial part of the ST segment is termed the J point (waveform 1 above).
- ❖ **Has a duration of 0.08 to 0.12 sec,**

- **The normal ST segment is usually flat along the isoelectric line** (i.e. zero potential as identified by the T-P segment) and has a slight upward concavity. However, it may have other configurations depending upon associated disease states (e.g. ischemia, acute MI, or pericarditis). In these situations, the ST segment may be flattened, depressed (below the isoelectric line) with an upsloping, horizontal, or down sloping morphology, or elevated in a concave or convex direction (above the isoelectric line).
- **ST elevation of greater than 2mm (> 2 small square) above the baseline or depression of greater than 1 mm (> 1 small square) below the baseline may be indicative of an MI**
- In some normal cases (as with sinus tachycardia) the J point is depressed and the ST segment is rapidly upsloping, becoming isoelectric within 0.08 seconds after the end of the QRS complex.
- *For more Look at ECG CRITERIA FOR MYOCARDIAL ISCHEMIA/INFARCT below*

D. T wave

- The T wave represents the period of **ventricular repolarization.**
- Since the rate of repolarization is slower than depolarization, the T wave is broad, has a slow upstroke, and rapidly returns to the isoelectric line following its peak (i.e. slow upstroke, rapid downstroke). Thus, the T wave is asymmetric and the **amplitude is variable.**
- In addition, the T wave is usually smooth up and down.
- **The duration is 0.08 to 0.12 sec (2-3 small boxes)**
- If there is any irregularity on the T wave (bump, notch, rippled, etc) a superimposed P wave should be considered.
- the T wave vector on the ECG normally is in the same direction as the major deflection of the QRS Since depolarization begins at the endocardial surface and spreads to the epicardium, while repolarization begins at the epicardial surface and spreads to the endocardium, the direction of ventricular depolarization is opposite to that of ventricular repolarization.
- Tall peaked T waves indicate hyperkalemia. Inverted T waves are suggestive of myocardial ischemia or a ventricular conduction delay. T waves that are larger or smaller than normal may indicate and electrolyte imbalance.

E. PR interval

- ✓ The PR interval includes the P wave as well as the PR segment.
- ✓ **It is measured from the beginning of the P wave to the first part of the QRS complex (which may be a Q wave or R wave).**
- ✓ It includes time for atrial depolarization (the P wave) and conduction through the AV node and the His-Purkinje system (which constitute the PR segment).
- ✓ **The length of the PR interval changes with heart rate, but is normally 0.12 to 0.20 sec (3 — 5 small boxes).**
- ✓ The PR interval is shorter at faster heart rates due to sympathetically mediated enhancement of atrioventricular (AV) nodal conduction; it is longer when the rate is slowed as a consequence of slower AV nodal conduction resulting from withdrawal of sympathetic tone or an increase in vagal inputs.

F. QT interval

- The QT interval consists of the QRS complex, the ST segment, and T wave. Thus, the QT interval is primarily a measure of ventricular repolarization.
- The JT interval, which does not include the QRS complex, is a more accurate measure of ventricular repolarization since it does not include ventricular depolarization, but in most clinical situations, the QT interval is used.
- If the QRS complex duration is increased, this will lead to an increase in QT interval but does not reflect a change in ventricular repolarization.
- A widened QRS, therefore, must be considered if a prolonged QT interval is being evaluated.
- The time for ventricular repolarization and therefore the QT (or JT) interval is dependent upon the heart rate; it is shorter at faster heart rates and longer when the rate is slower.
- Thus, a QT interval that is corrected for heart rate (QTc) is often calculated as follows (based on Bazett's formula):

$$\text{QTc} = \frac{\textbf{QT interval}}{\sqrt{\textbf{The RR interval (in sec)}}}$$

  - ✓ Although this approach is simple, it is inaccurate at heart rate extremes and results in overcorrecting at high rates and under correcting at low ones [1].
  - ✓ **The normal value for the QTc in men is ≤0.44 sec and in women is ≤0.45 to 0.46 sec.**
  - ✓ QTc values, however, are on a bell curve and normal patients may have longer QTc values, while those with Long QT syndrome may have shorter QT values.
  - Since the QRS widens in the setting of a bundle branch block, the QT interval will widen.
  - This increase in QT interval does not reflect an abnormality of ventricular repolarization, since the increase is due to an abnormality of depolarization.

G. U wave

- ➢ U wave may be seen in some leads, especially the precordial leads V2 to V4.
- ➢ The exact cause of this wave is uncertain, though data suggest it may be from late repolarization of the mid-myocardial M cells, due to a longer action potential duration compared with the endocardium or epicardium, especially at slow heart rates.
- ➢ The amplitude of the U wave is typically less than 0.2 mV and is clearly separate from the T wave. It is more evident in some circumstances such as hypokalemia and bradycardia.
- ➢ The U wave may merge with the T wave when the QT interval is prolonged (a QT-U wave), or may become very obvious when the QT or JT interval is shortened (eg, with digoxin or hypercalcemia).

6.5 APPROACH TO ECG INTERPRETATION

- A systematic approach to interpret an electrocardiogram (ECG) is essential for correct diagnosis
  - ✓ Step 1: Rate

- ✓ Step 2: Rhythm
- ✓ Step 3: Axis determination
- ✓ Step 4: Intervals
- ✓ Step 5: P wave
- ✓ Step 6: QRS complex
- ✓ Step 7: ST segment-T wave
- ✓ Step 8: Overall interpretation

1. Determining the Heart Rate

- A rate of 60 to 100 is considered normal. A rate less than 60 is bradycardia, while a rate over 100 is tachycardia
- There are two methods of determining heart rate
  - A. Rule of 300
  - B. 10 Second Rule

A. Rule of 300

- ❖ If the cardiac rhythm is regular, the interval between successive QRS complexes determined from the electrocardiogram (ECG) grid can be used to determine heart rate.
- ❖ The **division of 300 by the number of large boxes** calculates the heart rate/HR/.

$$\mathbf{HR} = \frac{\mathbf{300}}{\textbf{number of large boxes}\ \text{(between successive QRS complexes)}}$$

For example;

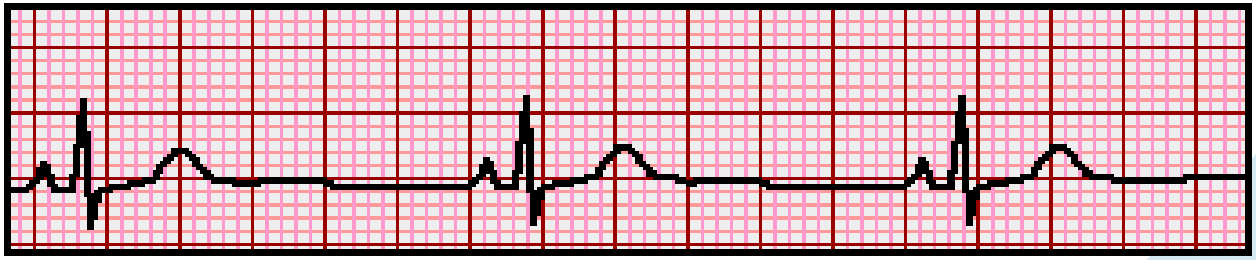
interval between two successive complexes	heart rate
1 large box	300 ÷ 1 = 300 beats/min
2 large boxes	300 ÷ 2 = 150 beats/min
3 large boxes	300 ÷ 3 = 1o0 beats/min
4 large boxes etc	300 ÷ 4 = 75 beats/min

- ❖ Alternatively, the time between QRS complexes can be measured in seconds. This number can be divided into 60 to derive the heart rate.

$$\mathbf{HR} = \frac{\mathbf{60}}{\textbf{time(in sec) between QRS complexes}}$$

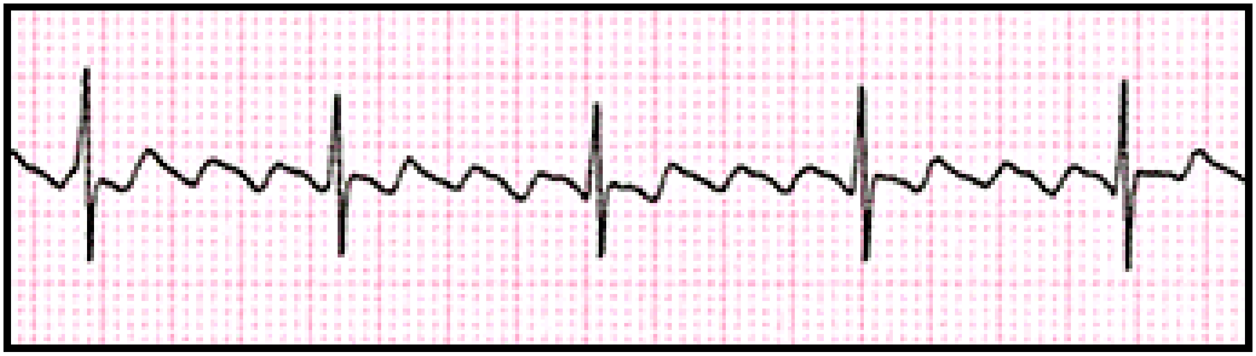
  - ✓ For instance, if the time between 2 QRS complexes is 0.75 seconds, the heart rate is 80 beats/min (60 seconds/minute ÷ 0.75 seconds/beat = 80 beats/min).
- ❖ **Although fast, this method only works for regular rhythms.**

Example 1



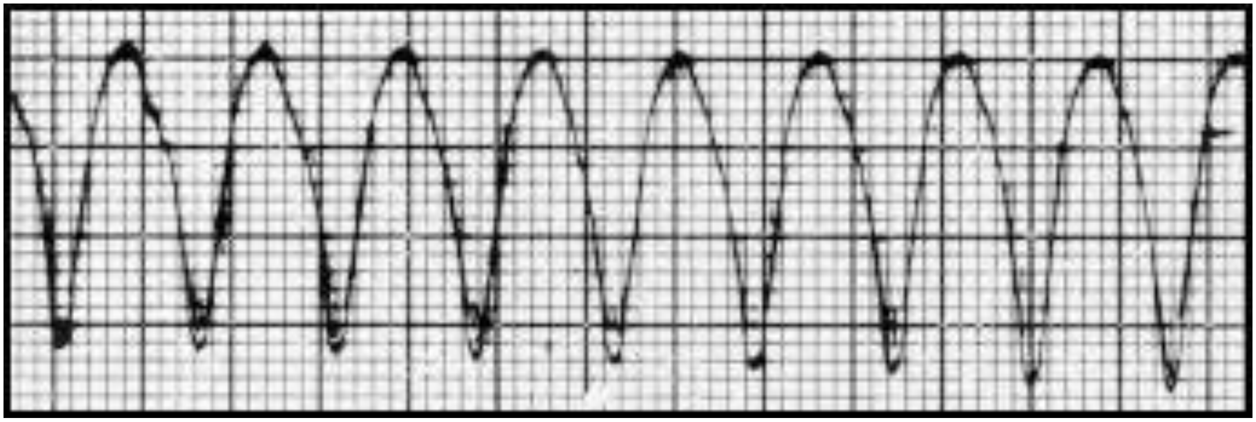
heart rate = 300 / 6 = 50 bpm

Example 2



heart rate = 300 / ~ 4 = ~ 75 bpm

Example 3

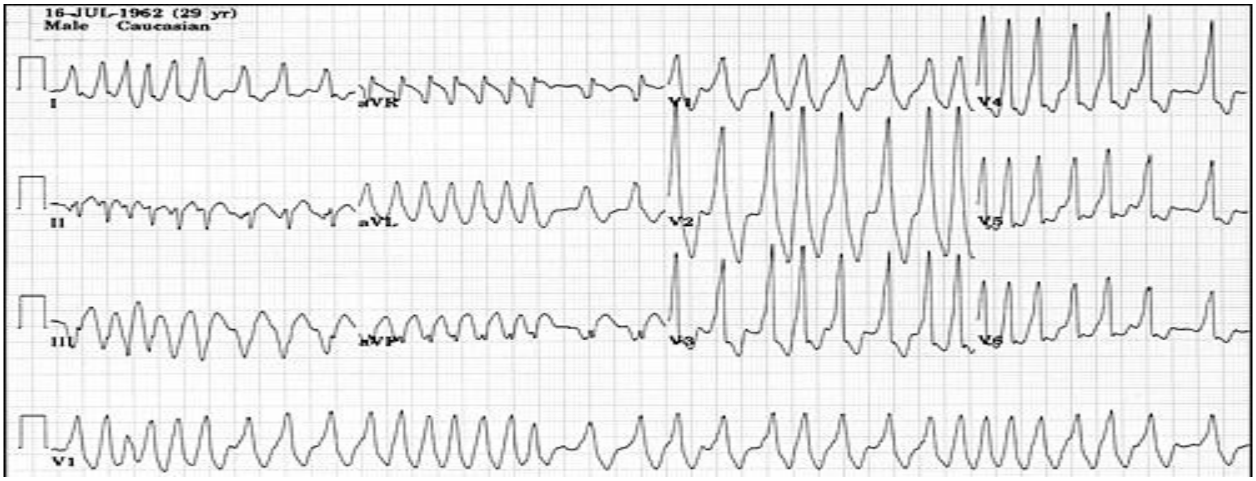


heart rate = 300 / 1.5 = 200 bpm

B. 10 Second Rule

- If the rhythm is irregular, the simplest way to determine the rate is by counting the number of complexes on the ECG and multiplying by six, since the standard ECG displays 10 seconds of time (As most EKGs record 10 seconds of rhythm per page).
  - ✓ **HR = 6 X total number of QRS complexes on the ECG**
- This method works well for irregular rhythms.

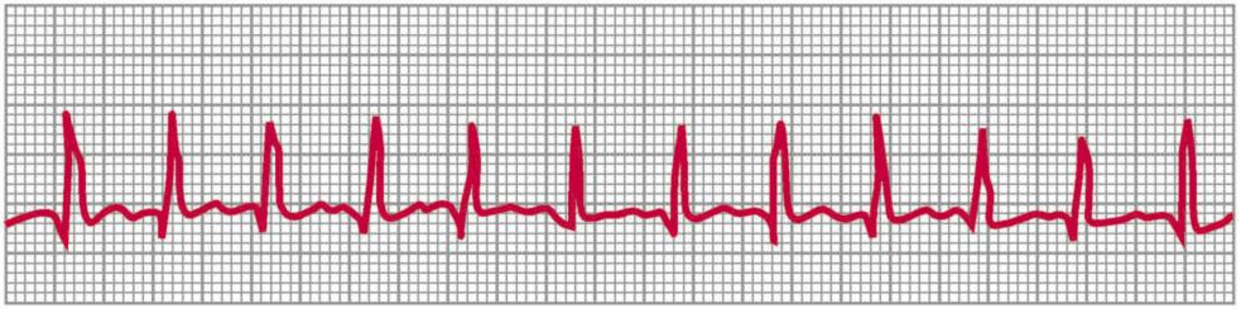
Example


16-JUL-1962 (29 yr)
Male Caucasian
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

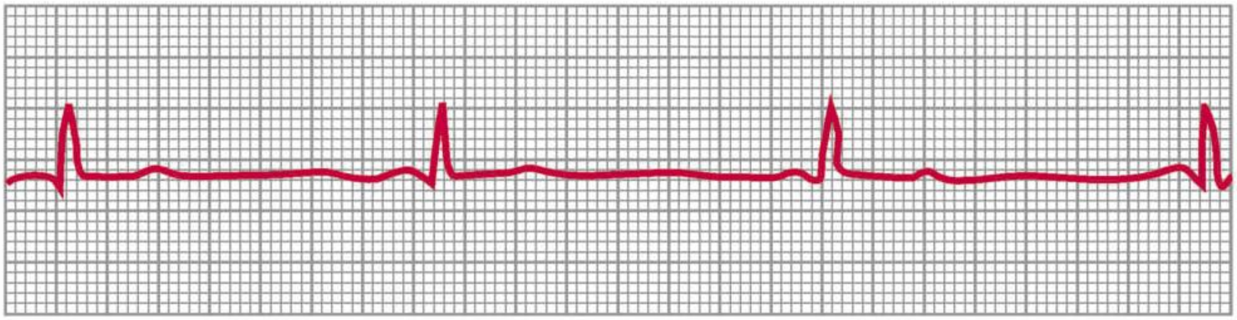
HR = 33 x 6 = 198 bpm

Regular rate abnormality examples

- Sinus tachycardia occurs at rates of 100 to 180
- Atrial tachycardia, AV nodal re-entrant tachycardia, or AV reciprocating tachycardia occur at rates of 140 to 220
- Atrial rates of 260 to 320 are seen with atrial flutter.



Sinus tachycardia (HR = 300 ÷ 1.5 = 200 bpm)



Sinus bradycardia (HR = 300 ÷ 7 = 43 bpm)

2. RHYTHM ANALYSIS

- ✓ Calipers are extremely helpful for rhythm analysis.
- ❖ **Step 1: Check the regularity of the QRS complexes**

- **Step 2: Locate the P wave**
- **Step 3: Establish the relationship between P waves and the QRS complex**

Step 1: check the regularity of the QRS complexes

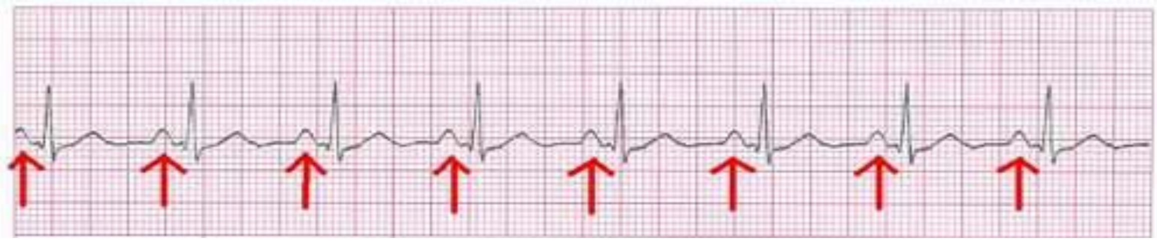
- Paper and Pencil Method
- Caliper Method

- Do the QRS complexes occur with regular intervals or are they irregular?

If the complexes are irregular

- ✓ Is there a pattern to the irregularity? Is the rhythm **regularly irregular** (i.e. there is a repeating pattern of irregularity) or is the rhythm **irregularly irregular** without any pattern of irregularity?
- ✓ At least 5 supraventricular rhythms are irregularly irregular:
  1. Sinus arrhythmia (in which there is only one P wave morphology and a stable PR interval)
  2. Sinus rhythm with premature atrial contractions
  3. Sinus or other rhythm with variable AV block
  4. Multifocal atrial rhythm (wandering atrial pacemaker) when the rate is <100 or multifocal atrial tachycardia with a rate >100 (in which there are ≥3 different P wave morphologies and PR intervals); or
  5. Atrial fibrillation (in which there is no organized electrical activity).

Step 2: Locate the P wave



- Are P waves visible? Are they regular?
  - ✓ Absence of P waves may occur secondary to atrial fibrillation.
  - ✓ Alternatively, P waves may be present but not visible if they are simultaneous with and buried within the QRS complex as in a junctional rhythm or atrioventricular (AV) nodal re-entrant tachycardia.
  - ✓ In addition, they may be located within the ST segment as with an AV reciprocating tachycardia or ventricular tachycardia.
  - ✓ If a P wave is halfway between two QRS complexes, a second P wave is often buried within the QRS complex.

Step 3: Establish the relationship between P waves and the QRS complex

- Are the P waves associated with QRS complexes in a 1:1 fashion? Do the P waves precede each QRS complex as is the case with most normal rhythms?
  - ✓ If not, are there more or less P waves than QRS complexes and what are the atrial and ventricular rates?

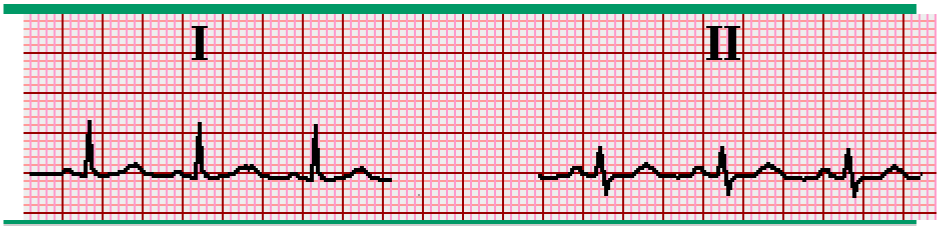
    - ✓ If there are **more P waves than QRS complexes**, then some form of **AV block** is present, which may be **physiologic if there is a concomitant atrial tachycardia or flutter.**
    - ✓ If there are **more QRS complexes than P waves**, then the rhythm is an **accelerated ventricular or junctional rhythm.**
- Do P waves occur after each QRS complex (i.e. retrograde P waves) What is the morphology? Are they upright or inverted? Are they all the same in shape and size? Are the irregular P waves associated with ectopic beats?
    - ♥ upright and rounded in lead II the P Waves are usually originating from the SA node, indicating a sinus rhythm.

A. Regular rhythm

Normal Sinus Rhythm

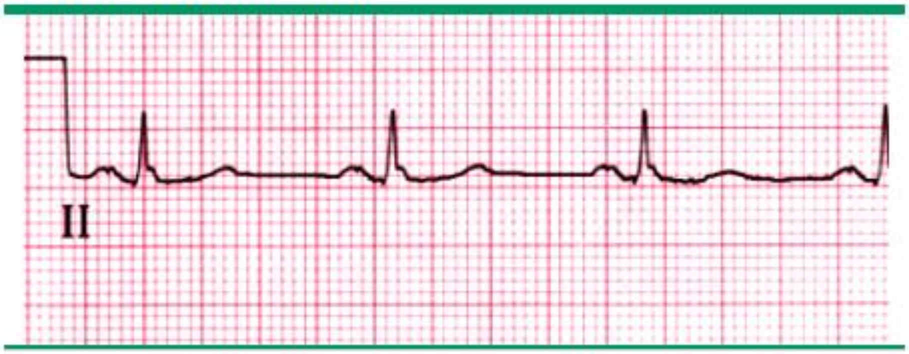
- Implies normal sequence of conduction, originating in the sinus node and proceeding to the ventricles via the AV node and His-Purkinje system.
- ECG Characteristics:
    - ✓ Rate 60-100 bpm
    - ✓ Regular narrow-complex rhythm
    - ✓ Each QRS complex is proceeded by a P wave
    - ✓ Narrow QRS complex
    - ✓ P wave is upright in lead II & down going in lead aVR

Sinus rhythm

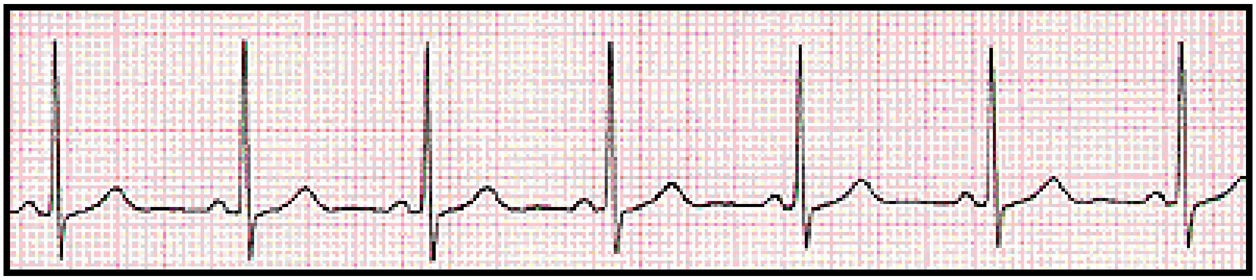


The normal P wave in sinus rhythm is slightly notched since activation of the right atrium precedes that of the left atrium. The P wave is upright in a positive direction in leads I and II. A P wave with a uniform morphology precedes each QRS complex. The rate is between 60 and 100 beats per minute and the cycle length is uniform between sequential P waves and QRS complexes. In addition, the P wave morphology and PR intervals are identical from beat to beat.

Normal rhythm strip



Normal rhythm strip in lead II. The PR interval is 0.15 sec and the QRS duration is 0.08 sec. Both the P and T waves are upright.



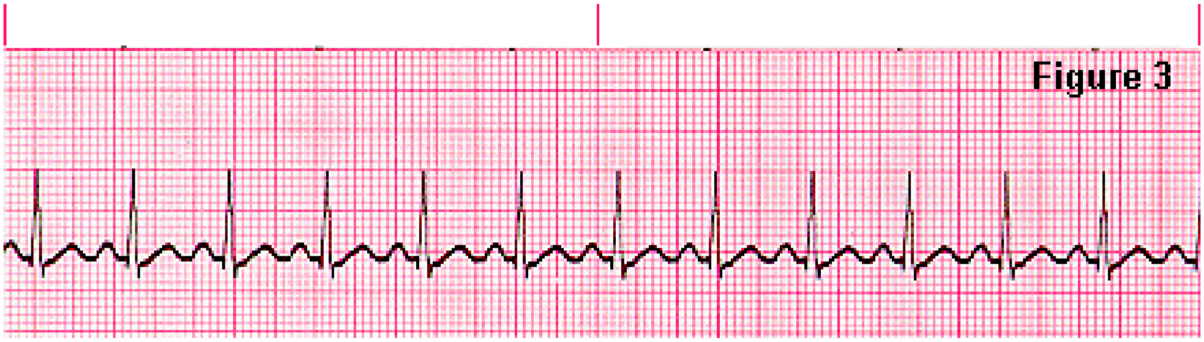
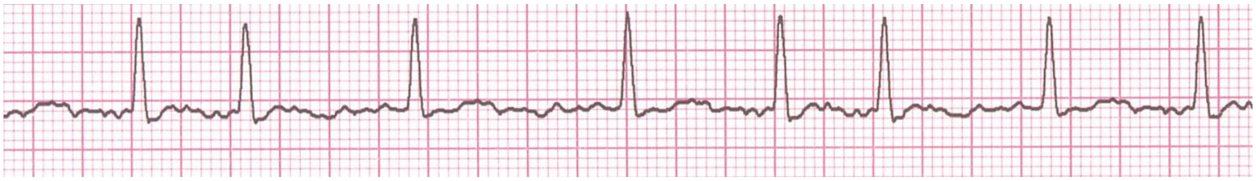
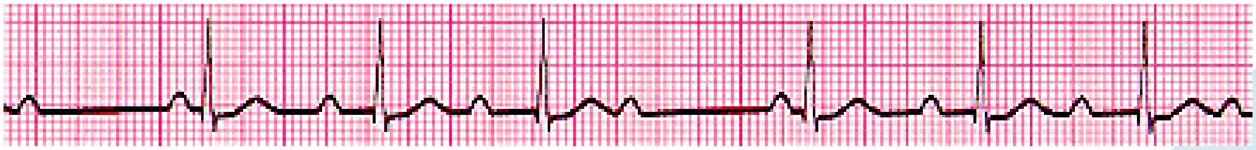
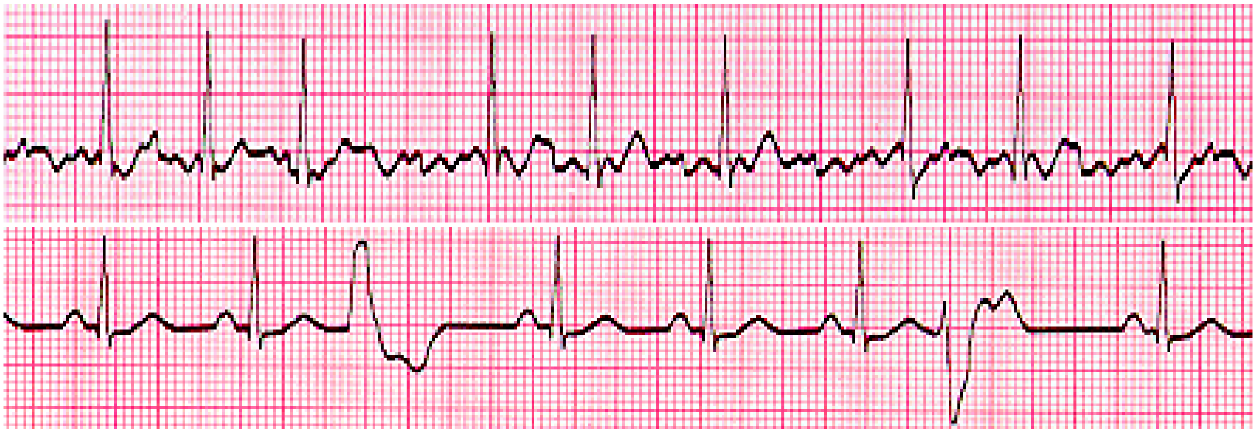


Figure 3



B. Irregular Rhythm



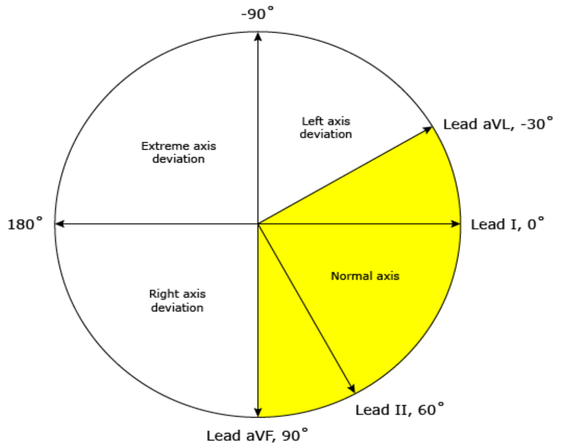


3. Axis determination

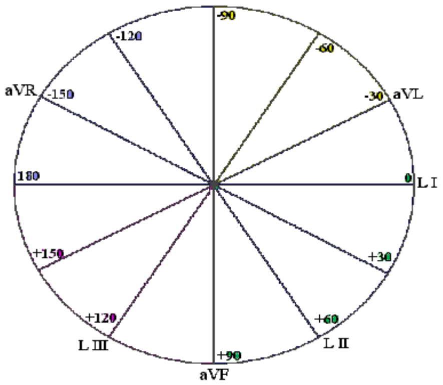
Axis

- Axis is the electrical signal recorded on the ECG which contains information relative to direction and magnitude of the various complexes.
- The normal QRS electrical axis, as established in the frontal plane, is between -30 and 90º (directed downward or inferior and to the left) in adults. /figure 1/
- An axis between -30º and -90º (directed superior and to the left) is termed left axis deviation.
- If the axis is between 90º and 180º (directed inferior and to the right), then right axis deviation is present.
- An axis between -90º and -180º (directed superior and to the right) is referred to as extreme right or left axis.
- If the QRS is equiphasic in all leads with no dominant QRS deflection, it is indeterminate axis.

Calculation of frontal plane axis


-90°
Left axis deviation
Lead aVL, -30°
Extreme axis deviation
180°
Lead I, 0°
Normal axis
Right axis deviation
Lead II, 60°
Lead aVF, 90°

If the QRS complex is positive in leads I and II, it falls between -30 and 90° and is normal, as indicated by the yellow area. If the QRS complex is negative in I and positive in aVF, there is right axis deviation. If the QRS complex is positive in I and negative in II, there is left axis deviation. If the QRS complex is negative in I and aVF, there is extreme axis deviation.


-90
-120
-60
aVR
-150
-30
aVL
180
0
L I
+150
+30
+120
+60
L III
L II
+90
aVF

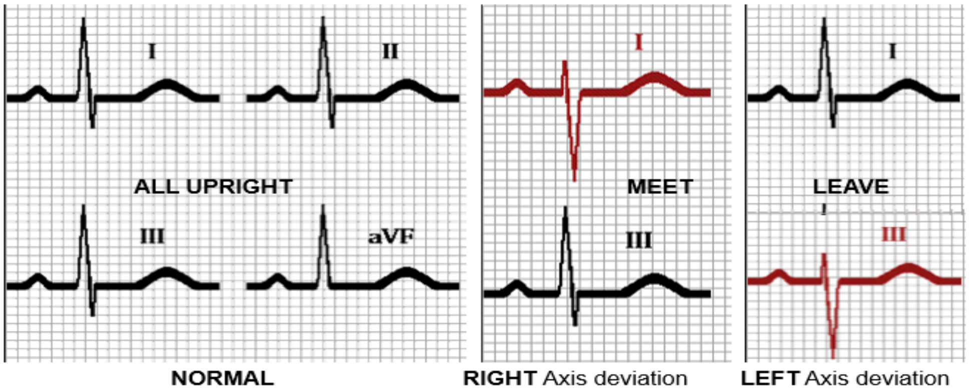
Normal Axis	-30 to +90	Right Axis	+90 to +180
Left Axis	-30 to -90	Indetermina	+180 to -90

figure 1

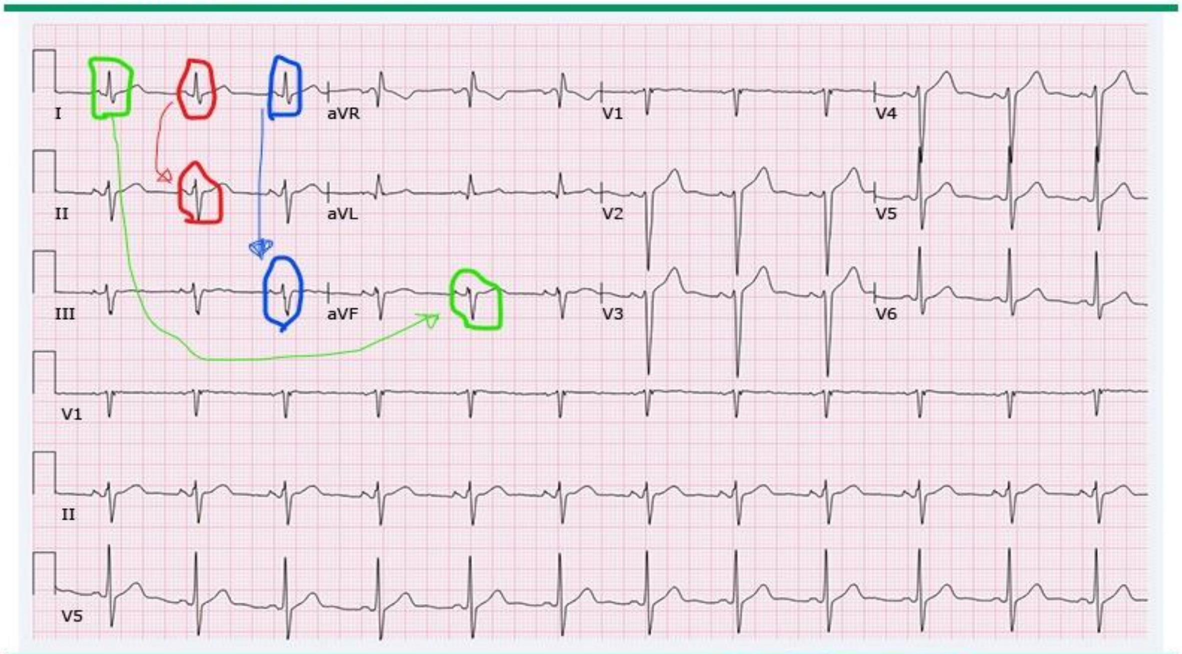
Axis Determination

- The QRS axis can be determined by examining all of the limb leads, but the easiest method involves looking at **leads I, II, and aVF only** (figure 2).
- If the **QRS complex is positive (upright) in both leads I and II**, then the axis falls between -30 and 90º, and the **axis is normal.**
- If the QRS complex is **positive in lead I** but **negative (down ward) in lead II**, then the axis is **leftward** (-30 to -90º).
- If the complexes are **negative in lead I and positive in aVF**, then the axis is **rightward** (90 to 180º).
- If the complexes are **negative in both I and aVF**, then the **axis is extreme** (180 to -90º).
- Another method of axis determination is to find the lead in which the complex is most isoelectric; the axis is directed perpendicular to this lead. As an example, if the QRS is isoelectric in lead III which is directed at 120º, then the electrical axis is either 30º or -150º.
- A third method is to determine the frontal lead in which the QRS is of the greatest positive amplitude. The axis is parallel to this lead.

Axis	**L_I**	**L_{II}**	**TIP**
Normal	Positive(upward)	Positive(upward)	Both Up
Right axis deviation (RAD)	Negative(downward)	Positive(upward)	Meet
Left axis deviation (LAD)	Positive(upward)	Negative(downward)	Leave
ERAD	Negative(downward)	Positive(upward)	Meet



ECG left anterior fascicular block



Sinus rhythm at 75 beats per minute. QRS duration is normal. Note the marked left axis deviation at about -60° consistent with left anterior fascicular block. As part of this pattern, qR is present in lead aVL along with terminal S waves in the lateral precordial leads. Slow R wave progression V1 through V3 is nondiagnostic.

figure 2

Table; summary of axis determination

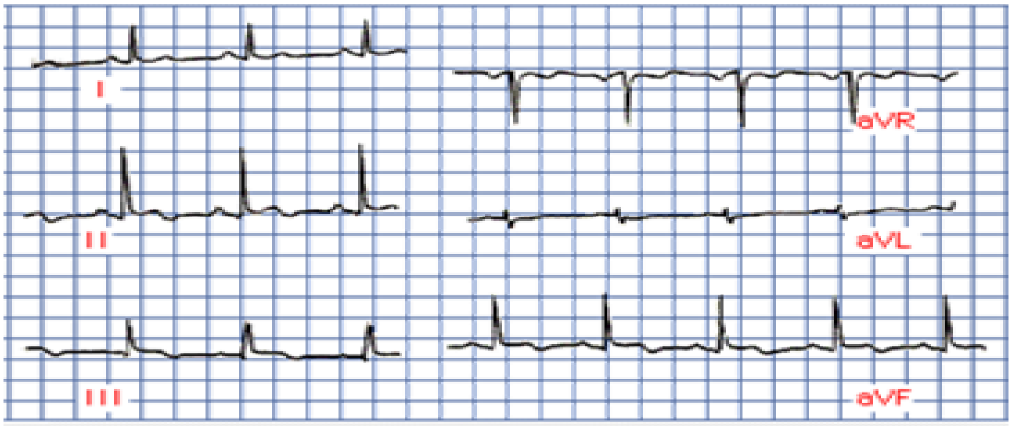
Mnemonics

- ♥ Leave criterion for LAD,
- ♥ The right thing is to meet each other (RAD)

Normal axis	Right axis deviation (RAD)	Left Axis Deviation (LAD)
♥ The QRS voltages are positive and upright in the leads - L1, L2, L3 and aVF ♥ L2, L3 and aVF tell that it is downward ♥ L1, aVL tell that it is to the left ♥ Downward and leftward is Normal Axis	♥ The QRS voltages are Down ward and Negative in L1, but positive and upright in leads L2, L3 and aVF. ♥ L2, L3 tell that it is downward ♥ L1 tells that it is to right ♥ Downward and rightward is Right Axis ♥ See the Right — Meet criterion of QRS in L1 and L3.	♥ The QRS voltages are positive and upright in leads L1 and aVL but Negative and down ward in L2, L3 and aVF ♥ L1, aVL tell that it is leftward ♥ L2, L3, and aVF tell that it is not down ward - instead it is upward ♥ Upward and Leftward is Left Axis ♥ See the Left - Leave each other criterion of QRS in L1 and L3.

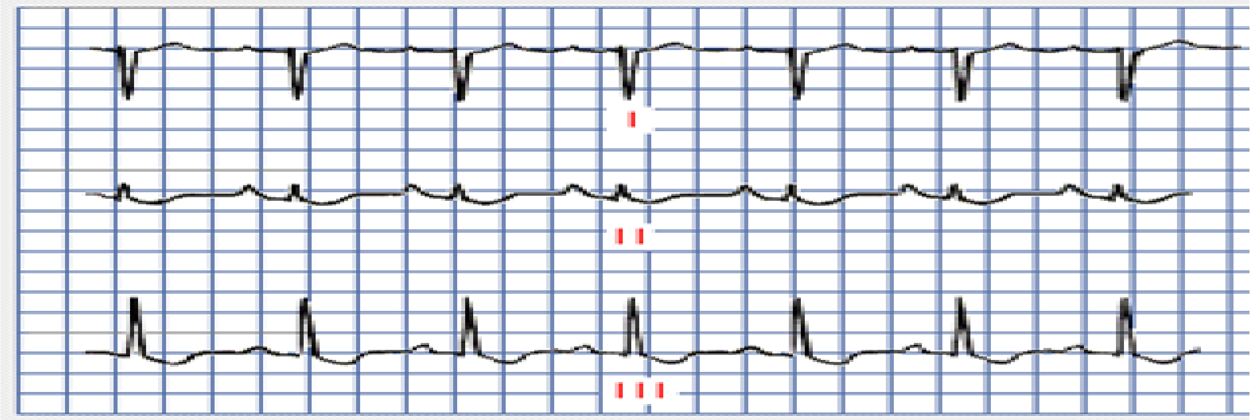
Determine the axis of the following ECG

Question 1



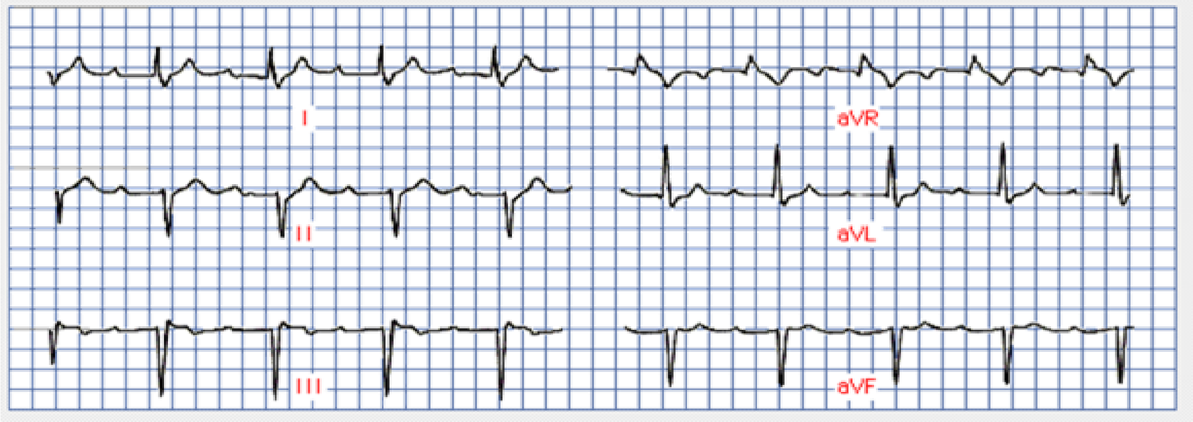
Answer; Normal axis

Question 2



Answer; Right axis deviation

Question 3



Answer; Left axis deviation

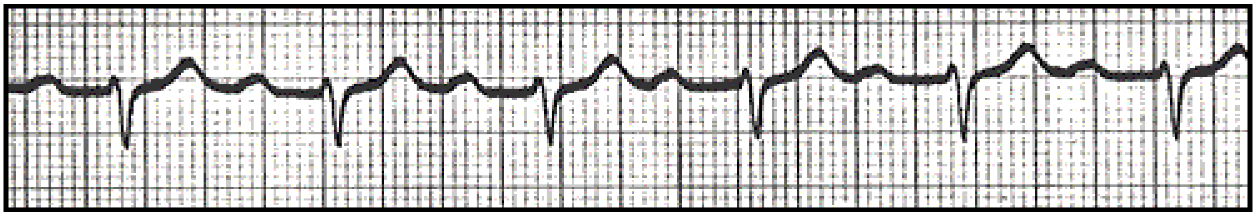
Causes of right axis deviation	Causes for left axis deviation
✓ Normal variation (vertical heart with an axis of 90º) ✓ Mechanical shifts, such as inspiration and emphysema ✓ RVH	✓ Normal variation (physiologic, often with age) ✓ Mechanical shifts, such as expiration, high diaphragm (pregnancy, ascites, abdominal tumor) ✓ LVH ✓ Left BBB

✓ Right BBB	✓ Inferior wall myocardial infarction.
✓ Lateral wall myocardial infarction	✓ Left anterior fascicular block
✓ Dextrocardia	✓ CHD (primum ASD, endocardial cushion defect)
✓ Ventricular ectopic rhythms	✓ Emphysema
✓ Secundum ASD	✓ Hyperkalemia
✓ Left posterior fascicular block	✓ Ventricular ectopic rhythms
✓ Pre-excitation syndrome (Wolff-Parkinson-White)	✓ Pre-excitation syndromes (Wolff-Parkinson-White)

4. Intervals

PR interval

- Normal PR interval: 0.12 to 0.20 s (3 - 5 small squares)
- A normal PR interval indicates the electrical impulse originated from the SA node or in the atrium.
- Short PR intervals are suggestive of Wolff-Parkinson-White syndrome.
- Long PR intervals are usually seen in first degree AV block, but there may be other causes.



Picture; Prolonged PR Interval

QRS interval

- Long QRS intervals represent a bundle branch block, ventricular pre-excitation, ventricular pacing, or ventricular tachycardia.

QT interval

- Short and long QT intervals may be present.

5. P wave

- See rhythm analysis above
- The normal sinus P wave is generally upright in leads I, II, aVF, and V4-V6 and negative in lead aVR. It may be negative or biphasic in leads III and V1.
- A negative P wave in the inferior leads or lead I suggests an ectopic rhythm (low atrial or left atrial respectively). Similarly, a completely positive P wave in V1 suggests a left atrial location.

6. QRS complex

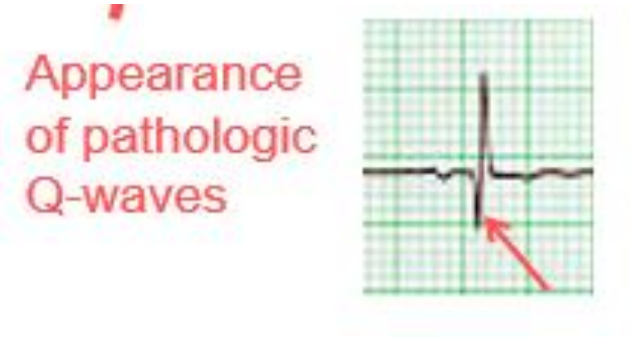
- It is essential to analyze the QRS in all 12 leads to be sure that it is normal.

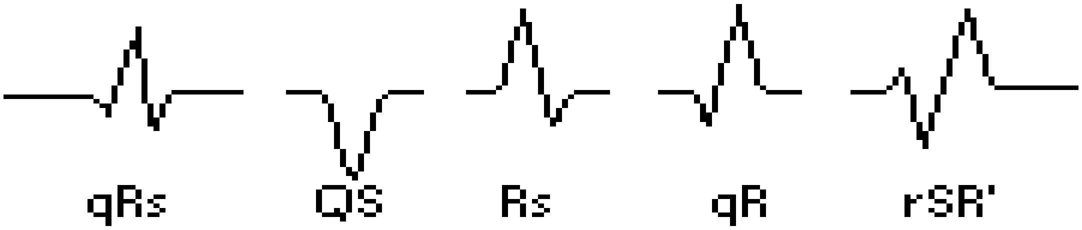
Look for

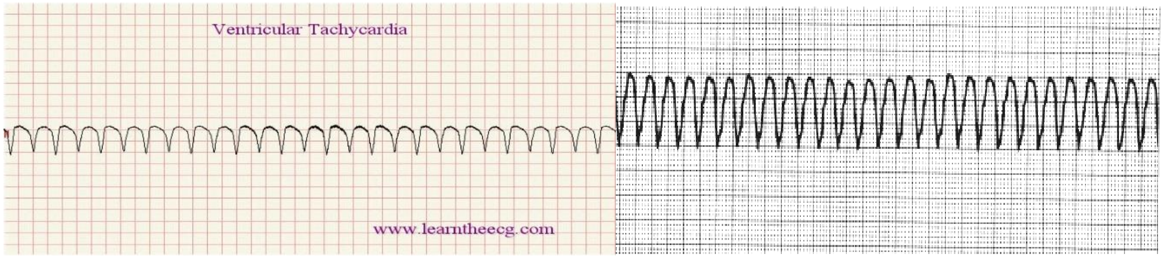
- ✓ QRS Axis
- ✓ Wide or narrow- duration normally lasts for 0.06 to 0.10 seconds (1½ to 2½ small boxes)
- ✓ Pathological Q waves
- ✓ Left or right ventricular hypertrophy
- ❖ If the QRS complexes are of normal duration (<0.10 sec) and morphology, then the rhythm is supraventricular.
- ❖ If the **QRS is wide** (i.e. >0.10 sec)
    - ✓ The rhythm is either supraventricular with aberrant conduction, pre-excitation, or ventricular pacing, or it is of ventricular origin.
    - ✓ Wide QRS with normal rate → **bundle branch block** (examination of the morphology can determine if there is left or right bundle branch block or pre-excitation present)
    - ✓ Regular wide QRS with tachycardia →**Ventricular tachycardia /hyperkalemia**
    - ✓ Wide QRS with increased voltage may indicate **left or right ventricular hypertrophy.**
- ❖ **A narrow QRS** complex (<0.06 sec) reflects rapid activation of the ventricles via the normal His-Purkinje system, which in turn suggests that the arrhythmia originates above or within the atrioventricular (AV) node (i.e., a **supraventricular tachycardia** [SVT]).

- ❖ Pathologic Q wave
    - ✓ By definition, a Q wave is an initially negative deflection of the QRS complex
    - ✓ 3 principles with respect to Q waves:
        1. Not all Q waves are pathologic
        2. Not all pathologic Q waves are due to myocardial infarction caused by fixed coronary artery occlusion; and
        3. There is no firm consensus on the criteria for the diagnosis of pathologic Q waves
    - ✓ **Prominent Q waves are a characteristic finding in myocardial infarction**, they can also be seen in a number of Non infarct settings such as;
        - ❖ Misplacement of chest lead electrodes
        - ❖ Dextrocardia
        - ❖ A rightward mediastinal shift in left pneumothorax
        - ❖ Pectus excavatum

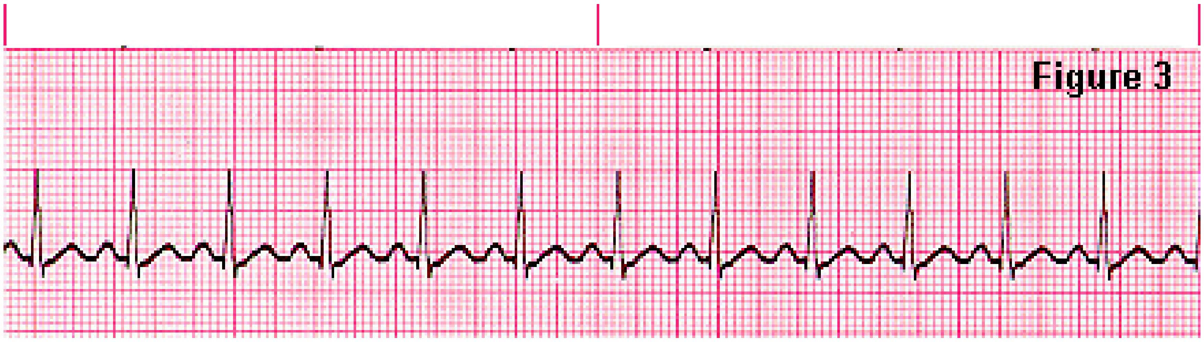
- COPD
- Rarely, congenitally corrected transposition of the great vessels or congenital absence of the left pericardium


Appearance of pathologic Q-waves


qRs
QS
Rs
qR
rSR'


Ventricular Tachycardia
www.learntheecg.com

Picture; QRS complex-wide like Ventricular tachycardia



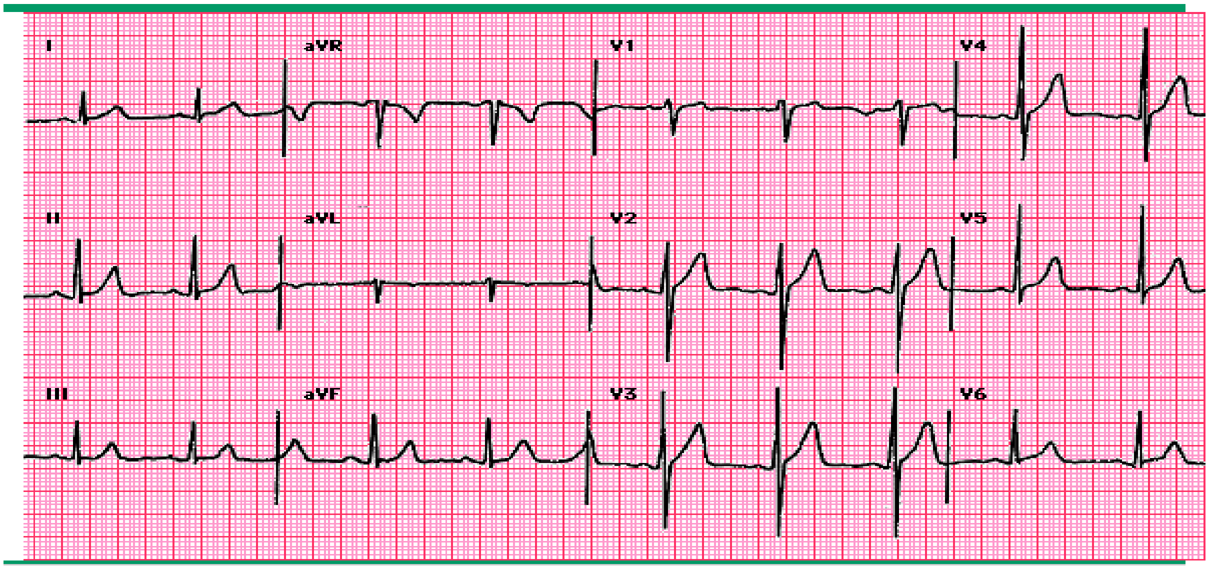
Picture; **Narrow QRS**

7. ST segment-T wave

- Is there ST elevation or depression compared to the TP segment?

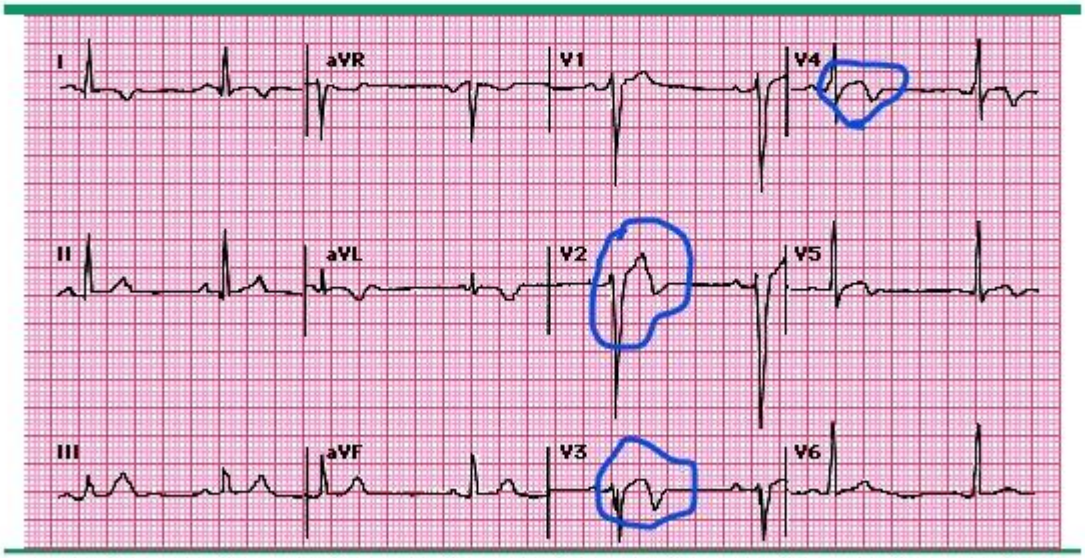
- The TP segment, between the T wave of one beat and the P wave of the next beat, should be used as the baseline.
- **Normal ST segment: No elevation or depression**
- ST segment has a duration of 0.08 to 0.12 sec,
- ST elevation greater than 2mm (>2 small squares) above the baseline or depression of greater than 1 mm (>1 small square) below the baseline may be indicative of an MI.

Normal ECG

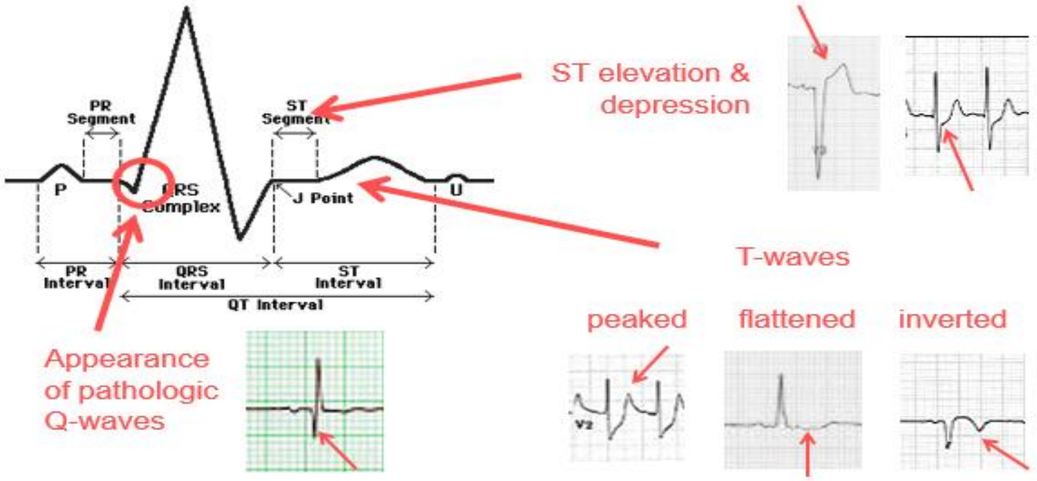


Normal electrocardiogram showing normal sinus rhythm at a rate of 75 beats/min, a PR interval of 0.14 sec, a QRS interval of 0.10 sec, and a QRS axis of approximately 75°.

Electrocardiogram (ECG) in an evolving anterior myocardial infarction



Electrocardiogram shows findings typical of an evolving Q-wave anterior MI: loss of R waves in leads V1 to V3, ST segment elevations in V2 to V4, and T wave inversions in leads I, aVL, and V2 to V5. Sinus bradycardia (55 beats/min) is present due to concurrent therapy with a beta blocker.


PR Segment
ST Segment
P
QRS Complex
J Point
U
PR Interval
QRS Interval
ST Interval
QT Interval
ST elevation & depression
T-waves
peaked
flattened
inverted
V2
Appearance of pathologic Q-waves

T wave

- Are the T waves inverted?
- High peaked T waves can be indicative of hyperkalemia.
- Inverted, elevated, or depressed T waves may indicate myocardial ischemia or injury.
- Inverted T waves are suggestive of MI or a ventricular conduction delay.
- T wave inversions due to evolving or chronic ischemia are often associated with QT prolongation.

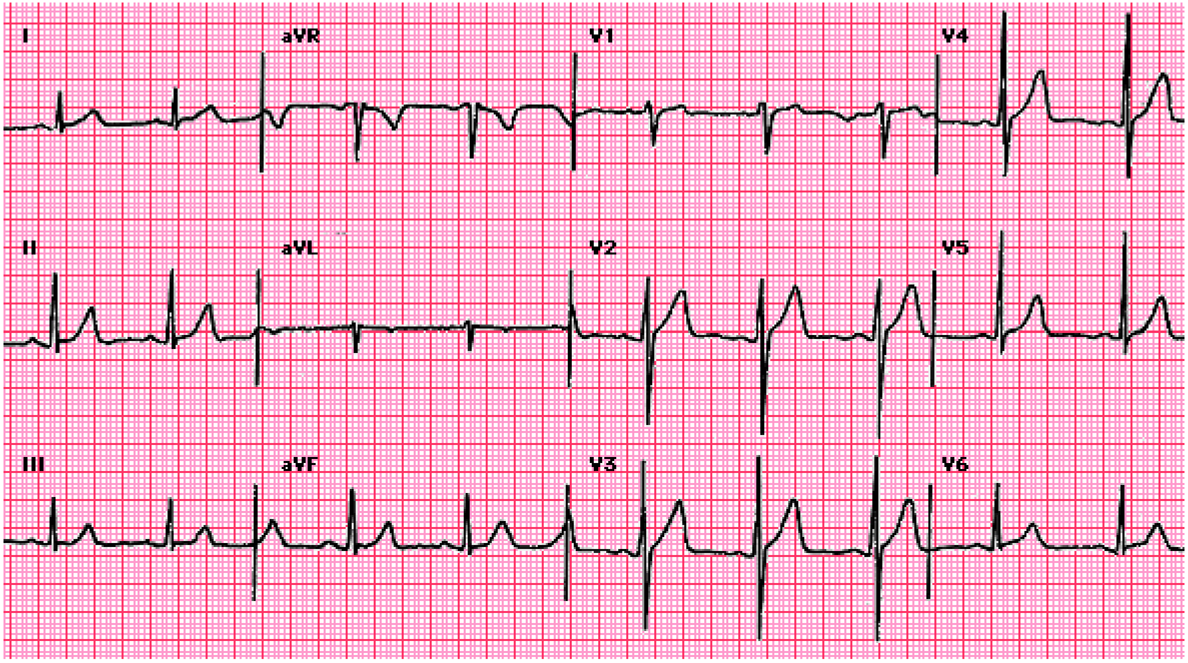
Causes of ST elevation	Causes of ST depression	Causes of tall T waves
✓ Acute MI (e.g. Anterior, Inferior, Lateral). ✓ LBBB or LVH (V1-V2 or V3) ✓ Acute pericarditis ✓ Normal variants (e.g. athletic heart) ✓ Abnormal early repolarization syndromes ✓ Other ❖ Myocarditis (may look like MI or pericarditis) ❖ Massive pulmonary embolism (leads V1-V2 in occasional cases) ❖ Brugada-type patterns (V1-V3 with right bundle branch block-appearing morphology) ❖ Myocardial tumor ❖ Myocardial trauma ❖ Hyperkalemia (only leads V1 and V2) ❖ Hypothermia (J wave/Osborn wave) ❖ Hypercalcemia (rarely) ❖ Post-DC cardioversion (rarely)	✓ Subendocardial MI ✓ Hypokalemia ✓ Digitalis toxicity	✓ Hyperkalemia ✓ Hyperacute MI ✓ LBBB

8. Overall interpretation

- Only after the prior steps have been completed should an overall description, interpretation and possible diagnoses be determined.
- This ensures assimilation of all information in the ECG and that no detail will be overlooked.

Example 1

Interpret the following ECG

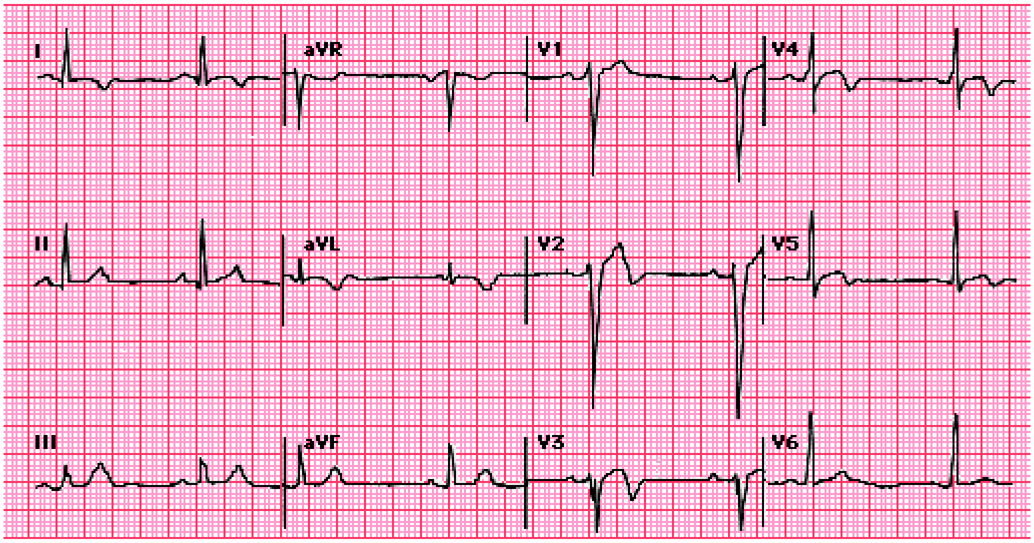


Answer;

- Rate = 75 bpm
- Regular sinus rhythm
- No axis deviation
- PR interval of 0.14 sec (3.5 small squares)
- Normal QRS complex (0.10 sec)
- No ST segment elevation or
- Normal T wave (No T wave inversion or tall T wave)

Index = Normal ECG

Example 2



Answer;

- Rate = 55 bpm
- Regular sinus rhythm
- No axis deviation
- PR interval of 0.12 sec (3 small squares)
- Loss of R waves in leads V1 to V3
- ST segment elevation in v2 to v4
- T wave inversion in leads I, aVL and V2 to V 5

Index = Anterior MI with sinus bradycardia

6.6 Common Disorders based on Pathologic finding from ECG

1. Myocardial ischemia and infarction
2. Pericarditis
3. Chamber hypertrophy
4. Arrhythmias
5. Electrolyte disturbances (i.e. hyperkalemia, hypokalemia)
6. Drug toxicity (i.e. digoxin and drugs which prolong the QT interval)

6.6.1 Myocardial Ischemia/infarction

Findings consistent with STEMI:

- ≥0.1 mV (1 mm) in all leads other than V2 and V3, where the following diagnostic thresholds apply:
    - ✓ ≥0.2 mV (2 mm) in men ≥ 40 years, ≥0.25 mV (2.5 mm) in men <40 years
    - ✓ ≥0.15 mV (1.5 mm) in women.

Findings consistent with NSTEMI or unstable angina: → in two anatomically contiguous leads

- New horizontal or down-sloping ST depression ≥0.05 mV (0.5 mm) or T inversion ≥0.1 mV (1 mm) with prominent R wave or R/S ratio >1.

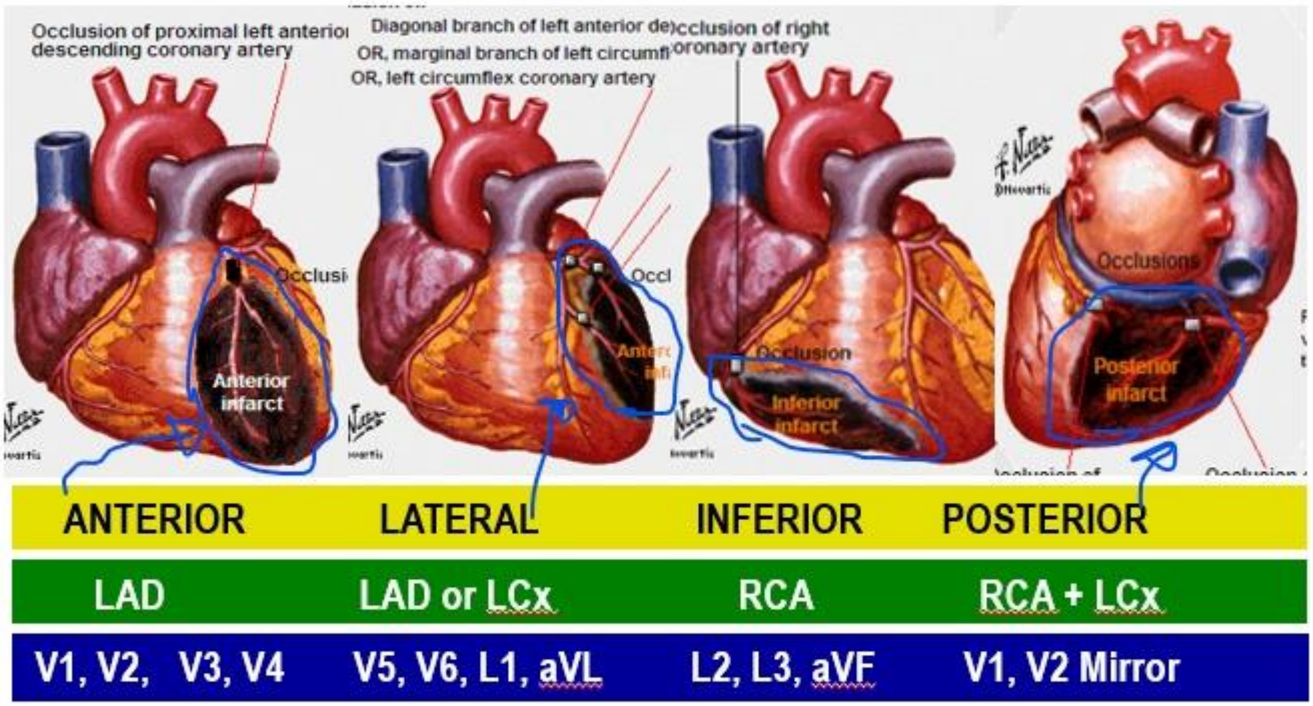
- Contiguous leads are defined as pairs or groups of leads that reflect the different walls of the heart. These are the **inferior (II, III, aVF), lateral (I, aVL), and anterior leads (V1 to V6).**

.

Prior MI

- the following are the criteria for ECG changes associated with **prior** MI (in the absence of LVH or LBBB)
- ♥ Any Q wave in leads V2 to V3 ≥0.02 sec or QS complex in V2 and V3; or Q wave ≥0.03 sec and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF; or V4 to V6 in any two leads of a contiguous lead grouping (I, aVL; V1 to V6; II, III, aVF).
- ♥ R wave ≥0.04 sec in V1 to V2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect.

LOCATION OF ISCHEMIA OR INFARCTION


Occlusion of proximal left anterioi descending coronary artery
Diagonal branch of left anterior de
OR, marginal branch of left circumfl
OR, left circumflex coronary artery
cclusion of right coronary artery
Occlusi
Anterior infarct
Occl
Anterc infa
Occlusion
Inferior infarct
Occlusions
Posterior infarct
ANTERIOR
LATERAL
INFERIOR
POSTERIOR
LAD
LAD or LCx
RCA
RCA + LCx
V1, V2, V3, V4
V5, V6, L1, aVL
L2, L3, aVF
V1, V2 Mirror

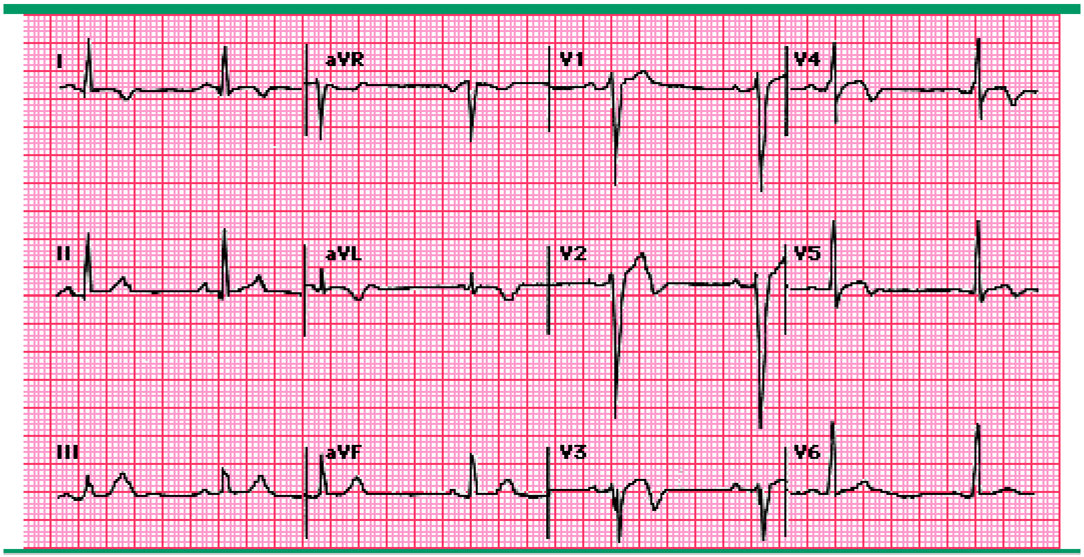
Image; blood supply and MI leads, LAD =left anterior descending coronary artery, RCA = right coronary artery, LCX = left circumflex coronary artery

- ♥ The portion of the LV that is ischemic or infarcted may be predicted by which ECG leads show ST-segment, T wave, or Q wave abnormalities.

A. Anterior, lateral, and apical MI

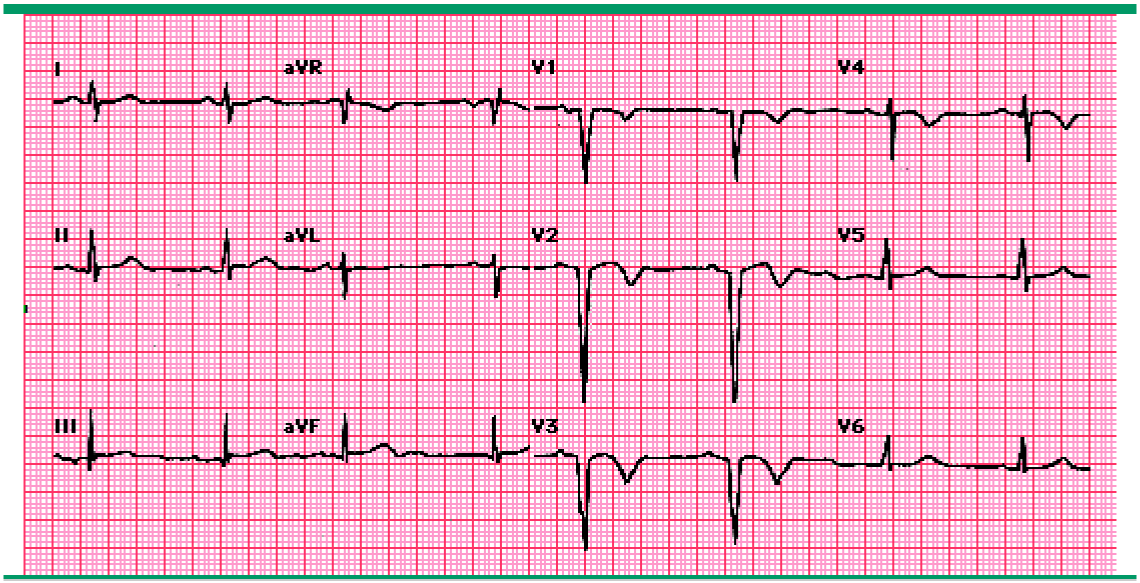
- ✓ ST-segment elevation or Q waves in one or more of the precordial leads (**V1 to V6**) and leads **I and aVL** has traditionally been used to suggest anterior wall ischemia or infarction (waveform 1A-B).
- ✓ Although characteristic ECG changes in leads **V1 to V3** are considered **typical of anteroseptal ischemia**, they **may be** more indicative of **apical ischemia.**

Electrocardiogram (ECG) in an evolving anterior myocardial infarction



Electrocardiogram shows findings typical of an evolving Q-wave anterior MI: loss of R waves in leads V1 to V3, ST segment elevations in V2 to V4, and T wave inversions in leads I, aVL, and V2 to V5. Sinus bradycardia (55 beats/min) is present due to concurrent therapy with a beta blocker.

Electrocardiogram (ECG) late in the evolution of an anterior myocardial infarction



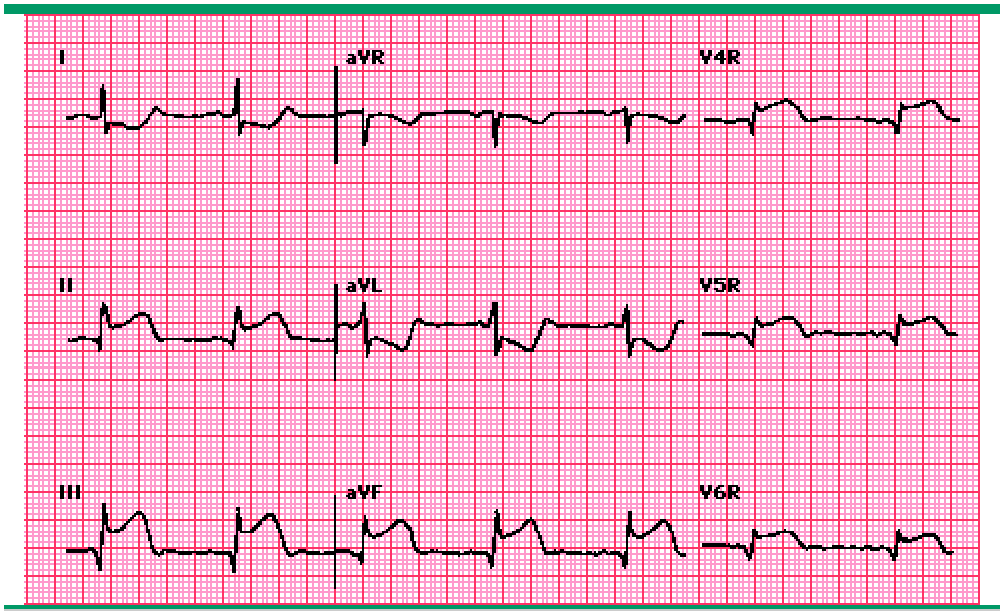
Later stage in the evolution of an acute anterior myocardial infarction. There is a QS pattern in leads V1 to V3 and T wave inversion in leads V2 to V4. The ST segment elevations in these leads have almost disappeared.

waveform 1A-B

B. Inferior and right ventricular MI

- ST-segment shifts or Q waves in leads **II, III, and aVF** suggest inferior wall ischemia or infarction (waveform 2).
- If there is evidence of inferior wall ischemia, right-sided leads, especially V3R and V4R, should be obtained to assess for a possible right ventricular ischemia/infarction (waveform 2).

ECG of acute inferior and right ventricular myocardial infarction

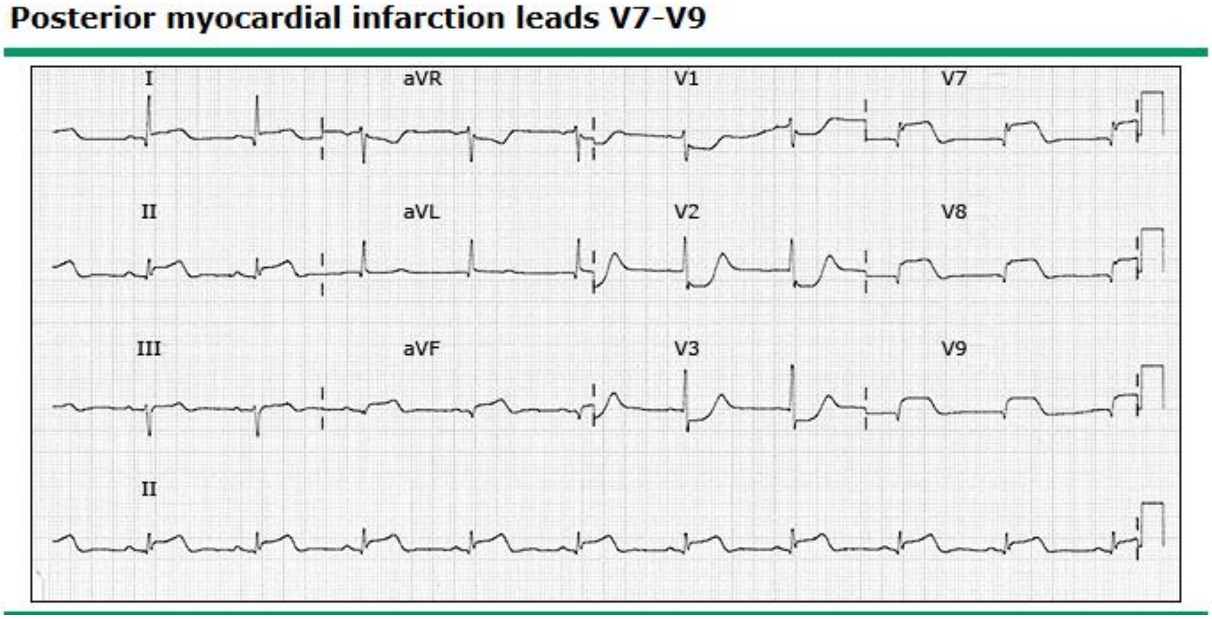


Electrocardiogram shows Q waves and prominent doming ST segment elevation in II, III, and aVF, findings which are characteristic of an acute inferior myocardial infarction. ST elevation in the right precordial leads - V4R, V5R, and V6R - indicates right ventricular involvement as well (arrows). The ST depressions in leads I and aVL represent reciprocal changes.

waveform 2

C. Posterior wall MI

- Acute posterior wall MI induces ST elevations in leads placed over the back of the heart, eg, leads **V7 to V9** (waveform 3 and figure 1).
- This is usually associated with **reciprocal ST—segment depression in leads V1 to V2 or V3.**
- Similar ST changes can also be the primary ECG manifestation of anterior subendocardial ischemia that may occur in combination with inferior infarction.
- Posterior inferior wall MI can usually be differentiated from anterior wall ischemia by the presence of ST-segment elevation in the inferior leads (II, III, aVF) in addition to posterior leads V7 to V9.
- Relatively tall R waves may also appear in leads V1 to V3 (waveform 4), corresponding to the appearance of pathologic Q waves (loss of depolarization forces) in the posterior leads.


Posterior myocardial infarction leads V7-V9
I
aVR
V1
V7
II
aVL
V2
V8
III
aVF
V3
V9
II

waveform 3

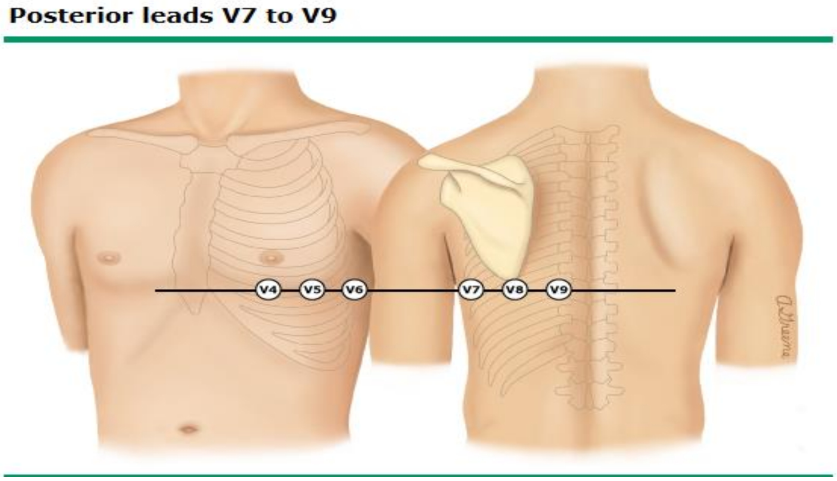
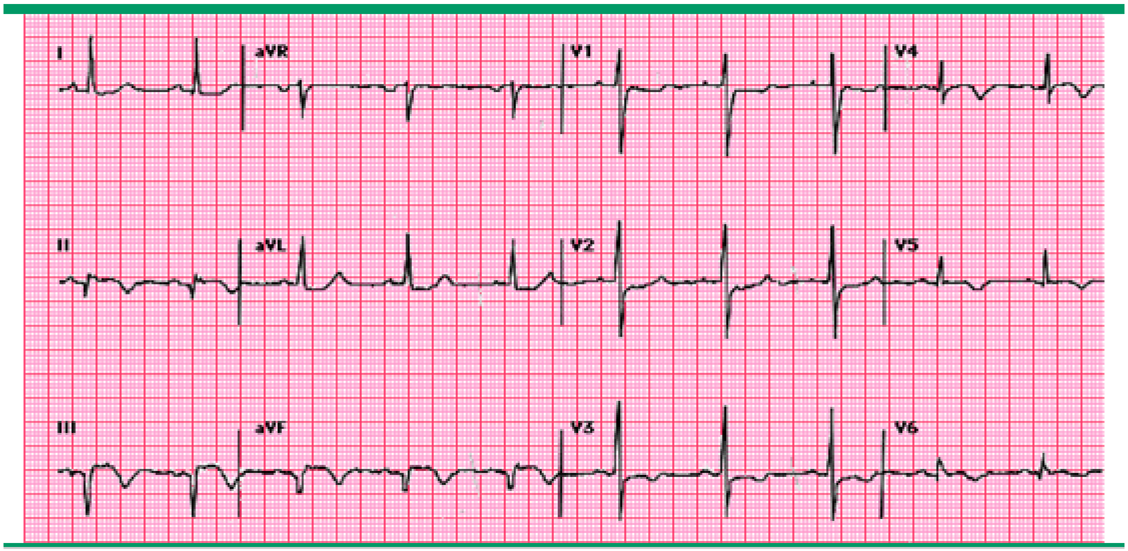

Posterior leads V7 to V9
V4
V5
V6
V7
V8
V9

figure 1

ECG acute infero-postero-lateral myocardial infarction



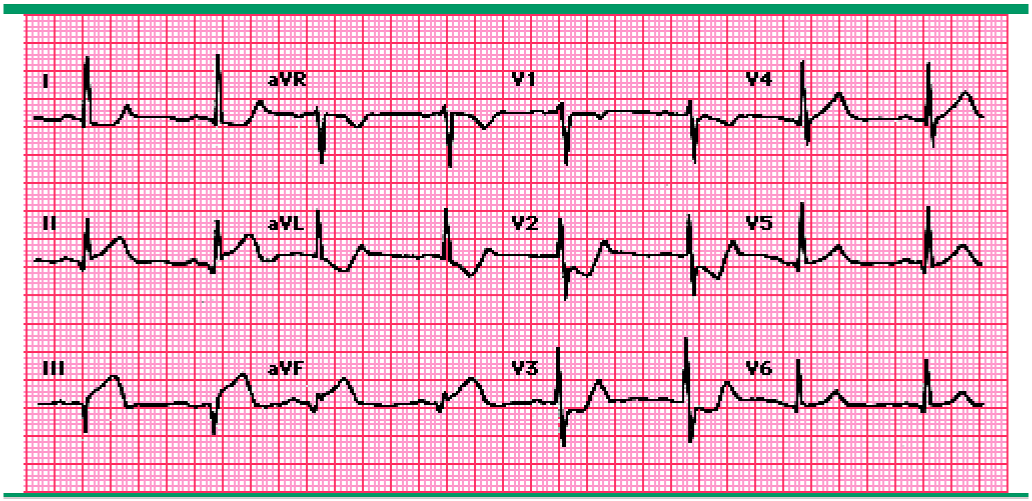
Electrocardiogram showing the major features of an inferior (Q waves, ST elevations, and T wave inversions in II, III, and aVF), posterior (tall R waves in V1 and V2), and lateral (T wave inversions in V4 to V6) myocardial infarction.

waveform 4

D. Multiple regions

- ♥ In some cases, ischemia affects more than one region of the myocardium.
- ♥ In this setting, the ECG should show the characteristic findings of involvement in each region (waveform 5). However, partial normalization may result from cancellation of opposing vectorial forces.

ECG of inferior MI with anterior ischemia

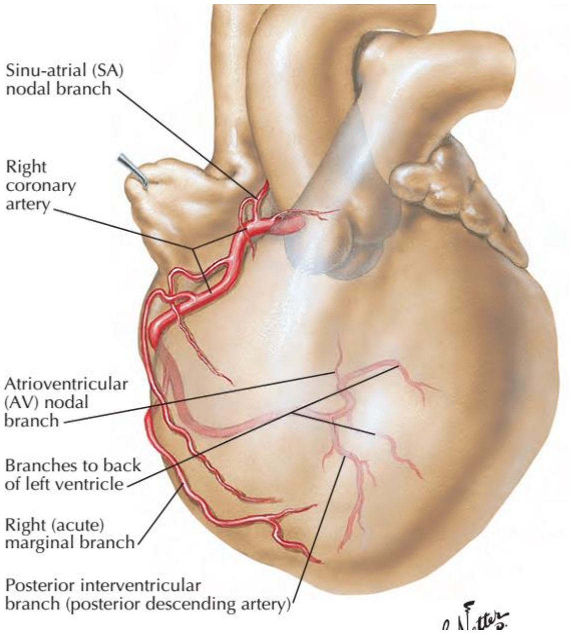


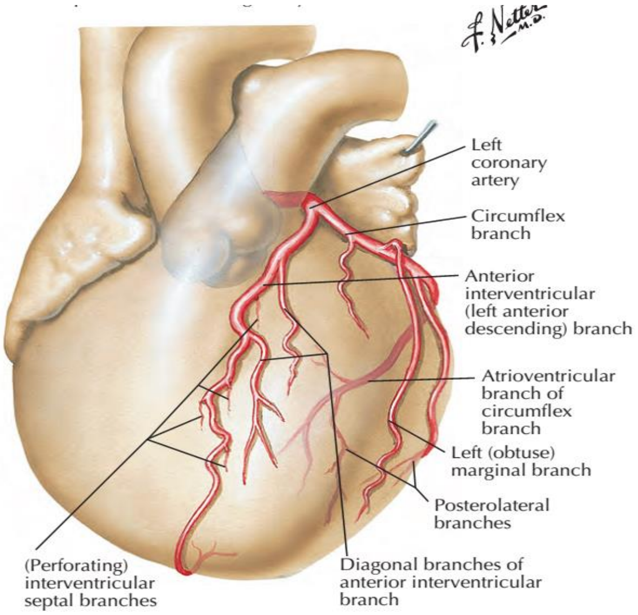
Electrocardiogram showing ischemic changes in two areas of the myocardium: inferior myocardial infarction (Q waves and ST elevations in leads II, III, and aVF); and anterior ischemia (ST depressions in leads V2 and V3).

waveform 5

IDENTIFICATION OF THE INFARCT-RELATED ARTERY

Blood supply of the heart


Sinu-atrial (SA) nodal branch
Right coronary artery
Atrioventricular (AV) nodal branch
Branches to back of left ventricle
Right (acute) marginal branch
Posterior interventricular branch (posterior descending artery)


Left coronary artery
Circumflex branch
Anterior interventricular (left anterior descending) branch
Atrioventricular branch of circumflex branch
Left (obtuse) marginal branch
Posterolateral branches
Diagonal branches of anterior interventricular branch
(Perforating) interventricular septal branches

- ✓ ECG may also provide information about the site or arterial occlusion in patients with STEMI.

Inferior MI on the ECG

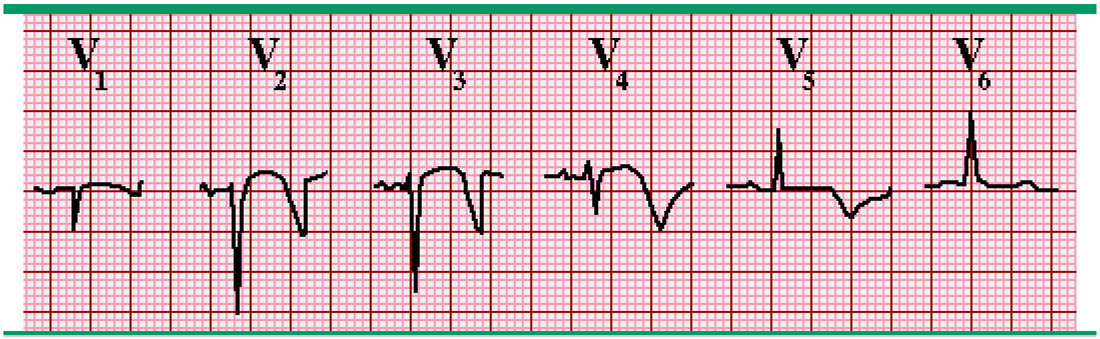
- ♥ An **inferior wall MI** generally have **occlusion of either the right or the left circumflex coronary artery.**
- ♥ The presence of **ST-segment elevation** in lead **III exceeding that in lead II**, particularly when combined **with ST-depression in leads I and aVL**, is a very useful predictor of an occlusion in the proximal or mid portion of the **right coronary artery**
- ♥ The presence of **ST-segment elevation in lead II**, which is equal to that of lead III, especially when combined **with ST-depression in leads V1 to V3 or ST-elevation in leads I and aVL**, is a useful but not absolute predictor of a **left circumflex coronary artery occlusion**; these findings may also be seen in distal occlusion of a dominant right coronary artery.
- ♥ Some patients with an inferior MI have right-sided ST-elevation in leads V1 and V4R; this finding is indicative of acute right ventricular injury and correlates closely with occlusion of the proximal right coronary artery.

Anterior MI on the ECG

- ♥ Anterior wall MI usually have occlusion of the **left anterior descending coronary artery (LAD).**
- ♥ The presence of ST-elevation in lead **aVR**, complete right bundle branch block, ST-depression in lead V5, and/or ST elevation in V1 greater than 2.5 mm strongly predicts a LAD artery occlusion proximal to the first septal perforator.

- Complete normalization of the ECG following STEMI is uncommon but can occur, particularly with smaller infarcts and when left ventricular ejection fraction and regional wall motion improve.
- Normalization is usually associated with spontaneous recanalization or good collateral circulation.
- In contrast, persistent Q waves and ST elevations several weeks or more after an infarct correlate strongly with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm (waveform 6).

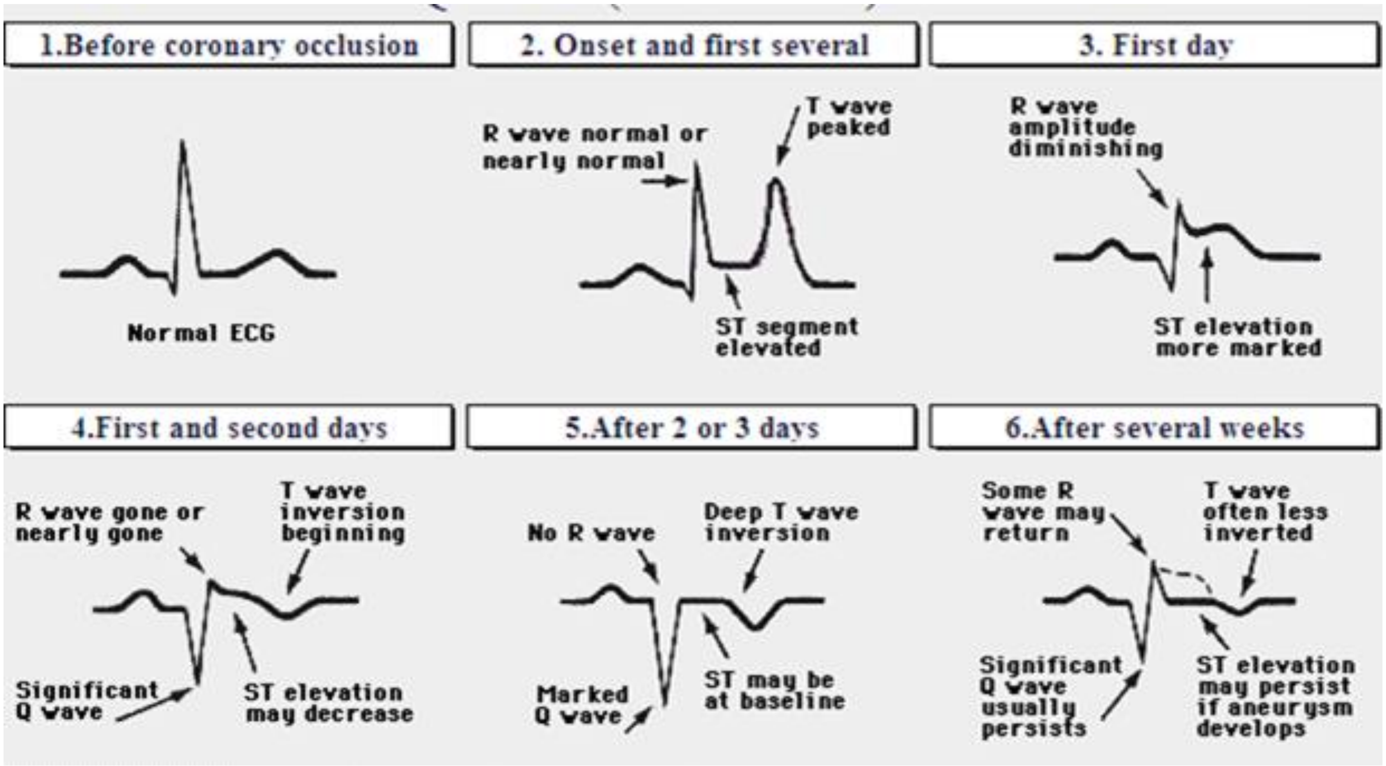
Persistent ST segment elevation post-MI



The presence of an anterior wall aneurysm following an acute myocardial infarction is suspected because of persistent ST elevation in leads V2 to V4. Inverted T waves are evidence of the old infarct.

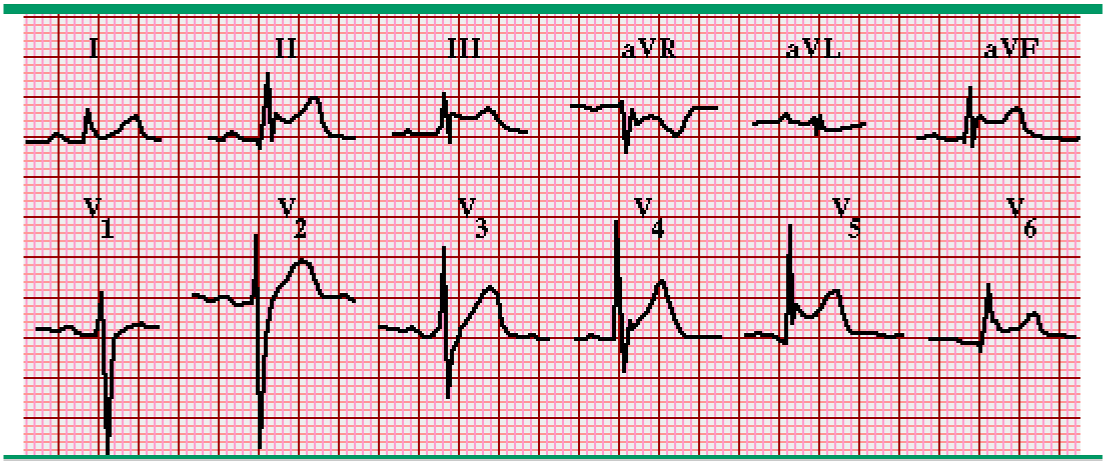
waveform 6

Serial ECG changes of MI


1.Before coronary occlusion
Normal ECG
2. Onset and first several
R wave normal or nearly normal
T wave peaked
ST segment elevated
3. First day
R wave amplitude diminishing
ST elevation more marked
4.First and second days
R wave gone or nearly gone
T wave inversion beginning
Significant Q wave
ST elevation may decrease
5.After 2 or 3 days
No R wave
Deep T wave inversion
Marked Q wave
ST may be at baseline
6.After several weeks
Some R wave may return
T wave often less inverted
Significant Q wave usually persists
ST elevation may persist if aneurysm develops

6.6.2 Pericarditis

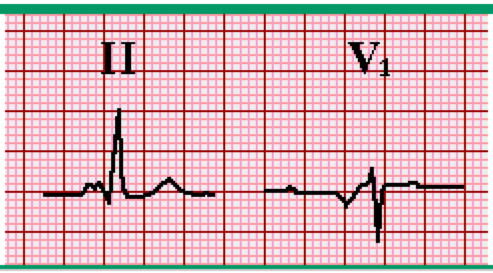
Pericarditis


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

J point and concave ST segment elevation seen diffusely in most of the precordial and limb leads are the hallmarks of pericarditis. There are no reciprocal ST changes. PR depression is evident in some leads.

6.6.3 Chamber enlargement and hypertrophy

Left atrial enlargement



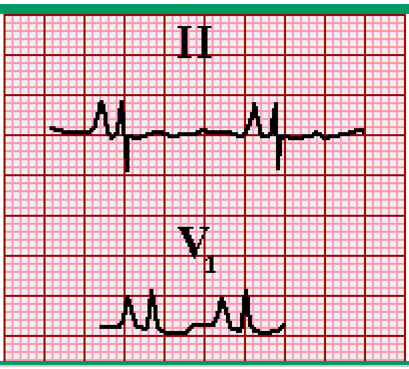
The P wave in lead II is broad and substantially notched, while V1 reveals a deeply inverted (negative) P wave.

- The following criteria suggest left atrial enlargement/abnormality when correlated with echocardiographic data:
  - **P wave duration >0.11 sec**
  - **P wave/PR duration >1.6**
  - Negative phase of P in V1 >0.04 sec or >1 mm
  - P-terminal force >0.04 mm/sec
  - Notched P, interpeak interval >0.04 sec

RIGHT ATRIAL ABNORMALITY/ENLARGEMENT

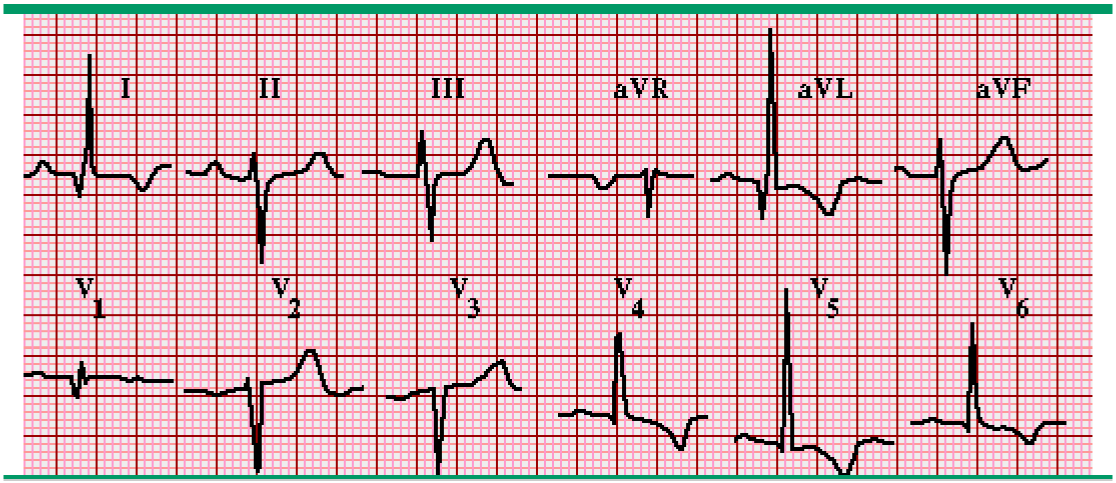
- A relatively narrow P wave that is of **increased amplitude** ("P pulmonale").
- The most common finding is a P wave >2.5 mm in lead II.
- In addition, a P wave >1.5 mm in V1 or V2 or a P wave that has a rightward axis may be seen.
- The amplitude of the P wave may become significantly increased
- If the right atrium becomes sufficiently large, it may extend toward the left, causing P waves in V1 to be inverted and giving the illusion of left atrial enlargement.
- In contrast to left atrial abnormality or interatrial block, the P wave duration is usually normal.

Electrocardiogram showing right atrial enlargement



Delayed activation of an enlarged right atrium leads to simultaneous activation of the right and left atria; this results in a relatively narrow P wave which is of increased amplitude.

Left ventricular hypertrophy

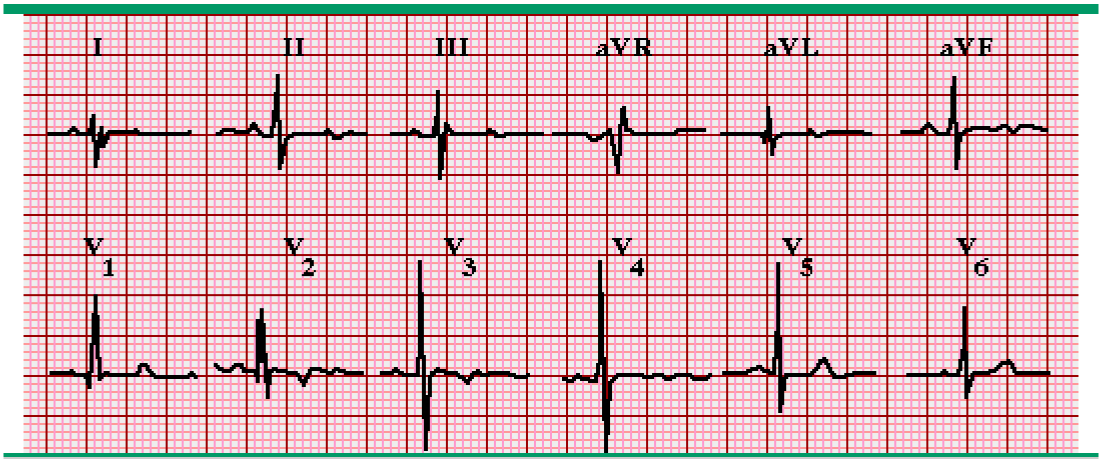


The electrocardiogram demonstrates a number of features of left ventricular hypertrophy (LVH). The QRS complex is slightly widened (about 0.11 sec), the frontal plane axis is leftward, tall R waves are present in multiple leads, and ST-T changes (formerly called a "strain" pattern) are present. The somewhat prominent P waves also raise consideration of left atrial abnormality. Slow R wave progression (V1-V3) is non-specific and may be seen with LVH, or with multiple other factors. Underlying anteroseptal MI is not excluded.

ECG criteria →There have been multiple ECG criteria proposed for diagnosing LVH. The most popular include:

- Amplitude of S wave in lead V1 + amplitude of R wave in V5 or V6 (whichever is the tallest) ≥35 mm.
- Amplitude of R wave in aVL + amplitude of S wave in V3 >28 mm for men, or >20 mm for women.
- QRS voltage in all leads >175 to 225 mm.
- R wave in I + S in 3 more than 25 mm
- R in aVL more than 11 mm or >18 mm if left axis is present
- R in aVF more than 20 mm
- S in aVR more than 14 mm
- S in V1 or V2 + R in V5 or V6 more than 35 mm
- R in V5 or V6 more than 26 mm
- R + S in any V lead more than 45 mm

Right ventricular hypertrophy

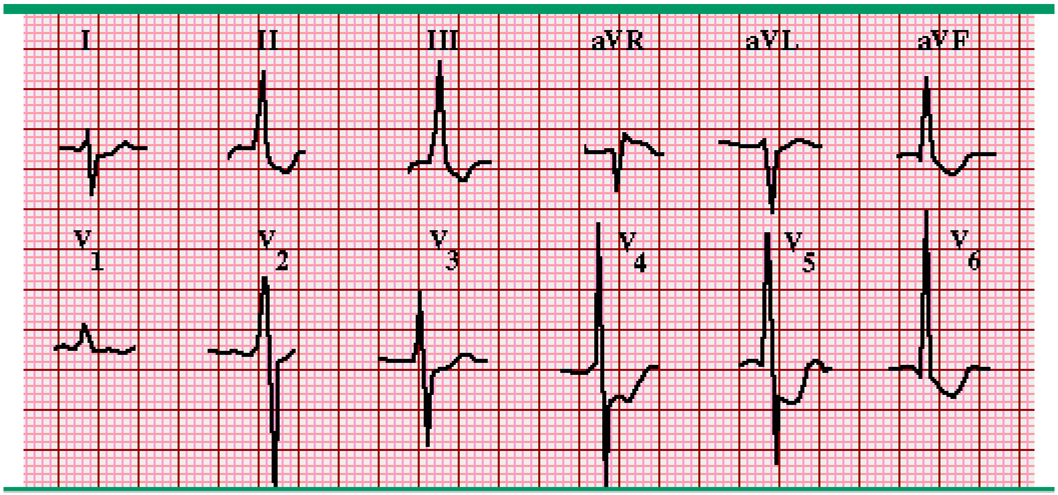


The right ventricular forces become predominant in patients with right ventricular hypertrophy (RVH), producing tall R waves in the right precordial leads (V1 and V2), and deep S waves in the left precordial leads (V5 and V6); an R:S ratio >1 in V1 and V2 is suggestive of RVH. Other features in this case include right axis deviation and RV1 >7 mm.

Clues to the diagnosis of right ventricular hypertrophy include:

- Right axis deviation (>+90)
- R in V1 >6 mm
- R in V1 + S in V5 or V6 >10.5 mm
- R/S ratio in V1 >1
- S/R ratio in V6 >1
- Late intrinsicoid deflection in V1 (>0.035 sec)
- Incomplete right bundle branch block
- ST-T wave abnormalities ("strain") in inferior leads
- Right atrial hypertrophy/overload (“P pulmonale”)
- S>R in leads I, II, III, particularly in children (S1S2S3 pattern)

Combined ventricular hypertrophy


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

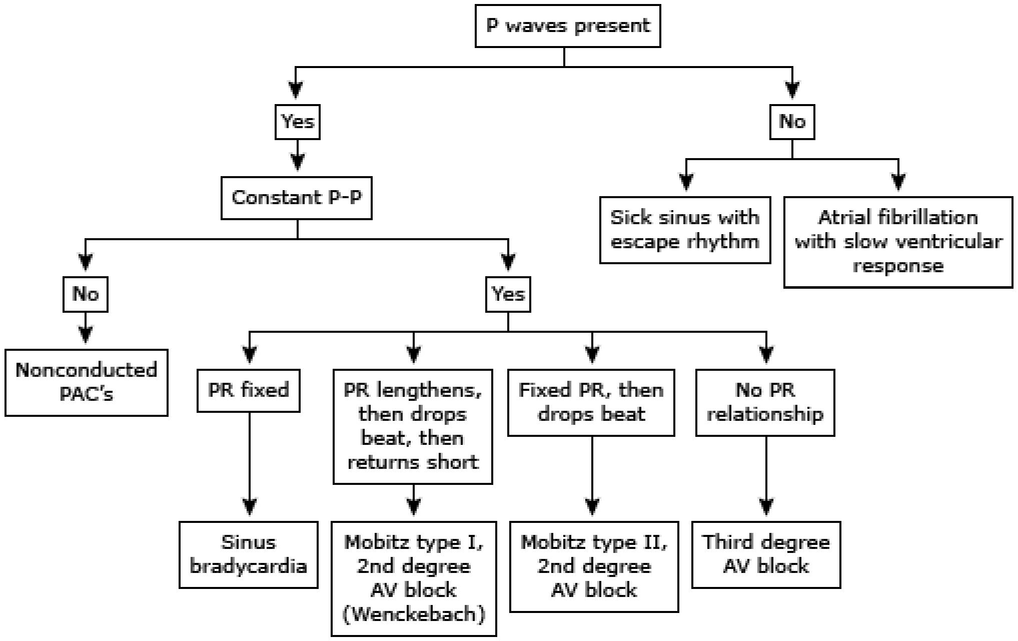
This ECG satisfies voltage criteria for left ventricular hypertrophy (S in V2 + R in V5 >35 mm), combined with a prominent R wave in V1 and right axis deviation (suggestive of right ventricular hypertrophy).

6.6.4 Arrhythmia

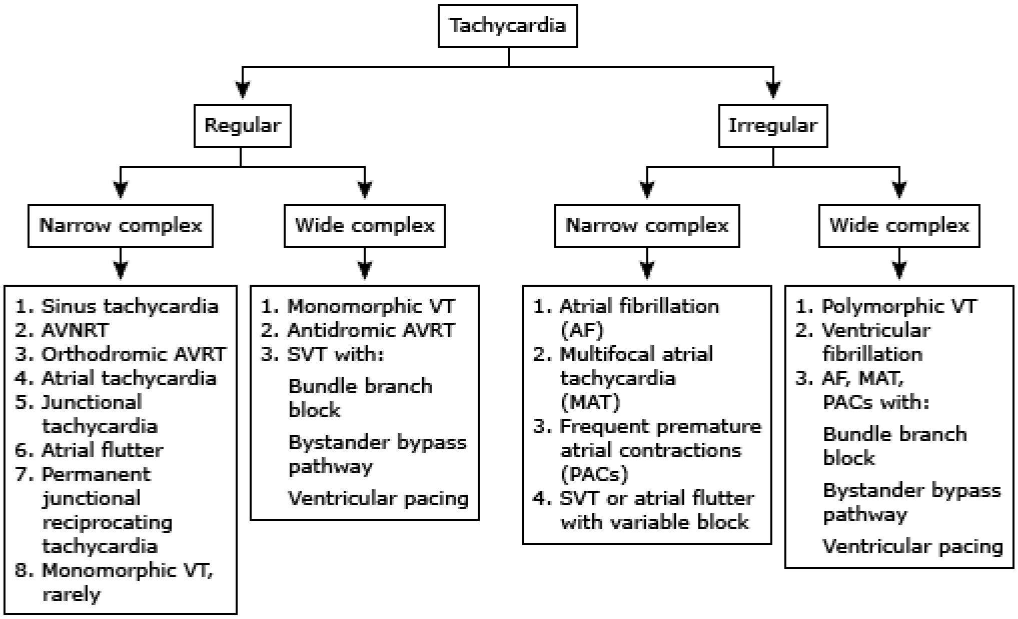
Mechanisms of Arrhythmias

- Altered Automaticity (Increased or decreased Automaticity)
- Reentry from ectopic foci
- Triggered activity
- Conduction Block

Approach to bradycardia


P waves present
Yes
No
Constant P-P
Sick sinus with escape rhythm
Atrial fibrillation with slow ventricular response
No
Yes
Nonconducted PAC's
PR fixed
PR lengthens, then drops beat, then returns short
Fixed PR, then drops beat
No PR relationship
Sinus bradycardia
Mobitz type I, 2nd degree AV block (Wenckebach)
Mobitz type II, 2nd degree AV block
Third degree AV block

Approach to tachycardia


Tachycardia
Regular
Irregular
Narrow complex
Wide complex
Narrow complex
Wide complex
1. Sinus tachycardia
2. AVNRT
3. Orthodromic AVRT
4. Atrial tachycardia
5. Junctional tachycardia
6. Atrial flutter
7. Permanent junctional reciprocating tachycardia
8. Monomorphic VT, rarely
1. Monomorphic VT
2. Antidromic AVRT
3. SVT with:
Bundle branch block
Bystander bypass pathway
Ventricular pacing
1. Atrial fibrillation (AF)
2. Multifocal atrial tachycardia (MAT)
3. Frequent premature atrial contractions (PACs)
4. SVT or atrial flutter with variable block
1. Polymorphic VT
2. Ventricular fibrillation
3. AF, MAT, PACs with:
Bundle branch block
Bystander bypass pathway
Ventricular pacing

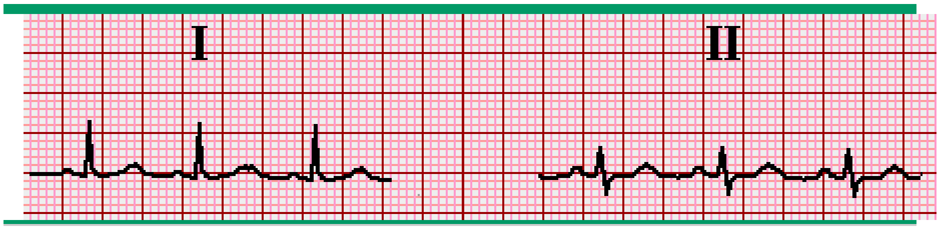
SVT = Supraventricular tachycardia, PVCs = premature ventricular contractions, AVNRT = Atrioventricular node reentry tachycardia, AVRT = Atrioventricular reentrant tachycardia. VT = Ventricular Tachycardia

Tachyarrhythmias

- Supraventricular tachycardia (SVT)
- Atrial fibrillation
- Atrial flutter
- Ventricular tachycardia
  - ✓ Monomorphic
  - ✓ Polymorphic (Torsade's de pointe)
- Ventricular fibrillation

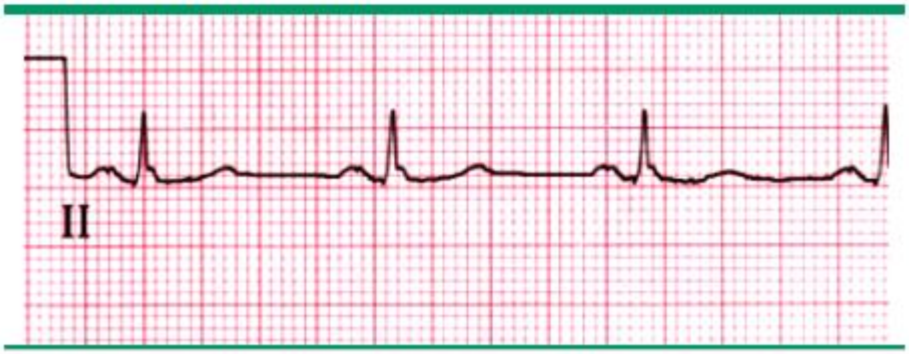
Rhythms and arrhythmias of the sinus node

Sinus rhythm



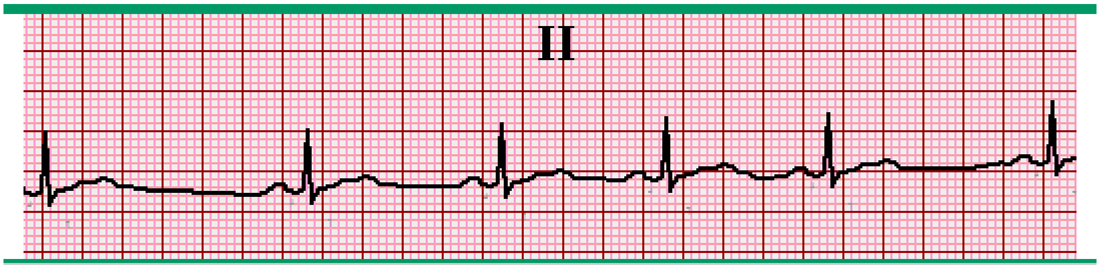
The normal P wave in sinus rhythm is slightly notched since activation of the right atrium precedes that of the left atrium. The P wave is upright in a positive direction in leads I and II. A P wave with a uniform morphology precedes each QRS complex. The rate is between 60 and 100 beats per minute and the cycle length is uniform between sequential P waves and QRS complexes. In addition, the P wave morphology and PR intervals are identical from beat to beat.

Normal rhythm strip



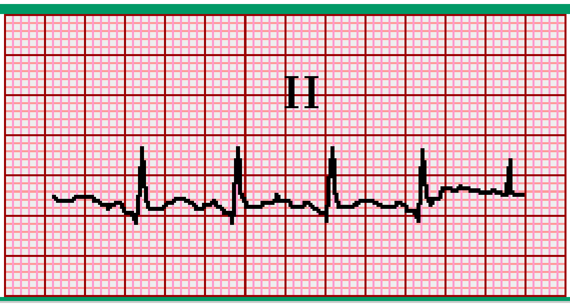
Normal rhythm strip in lead II. The PR interval is 0.15 sec and the QRS duration is 0.08 sec. Both the P and T waves are upright.

Sinus arrhythmia



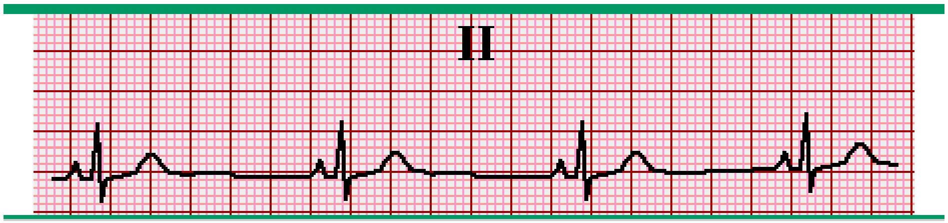
Sinus arrhythmia is present when there is a sinus rhythm with variability in the cycle lengths between successive P waves. This rhythm strip reveals a gradual increase and decrease in the heart rate with the respiratory cycle; the heart rate increases with inspiration and decreases with expiration.

Sinus tachycardia



Sinus tachycardia is defined as a sinus rhythm with a rate of greater than 100 beats per minute and less than approximately 160 to 180 beats per minute. In this tracing, the rate is about 130 beats per minute.

Sinus bradycardia

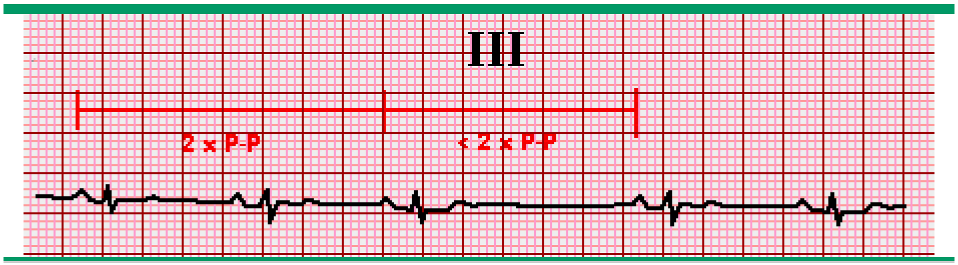


Sinus bradycardia is defined as a sinus rhythm with a rate less than 60 beats per minute. This rhythm strip shows a sinus rate of 50 beats per minute.

Table; possible reversible causes of sinus bradycardia **(the H &T s)**

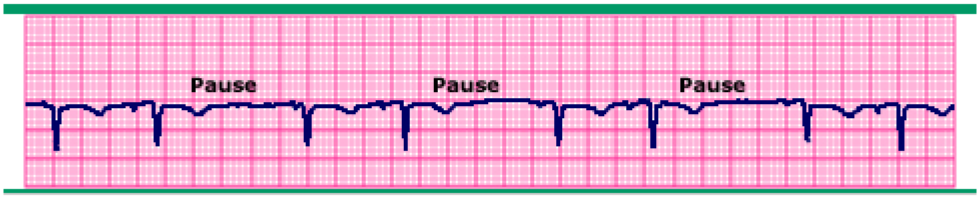
H's	T's
♥ Hypoxia ♥ Hypovolemia ♥ H+ (acidosis) ♥ Hypo/hyperkalemia ♥ Hypo/hyperglycemia ♥ Hypo/hyperthermia	♥ Toxins (overdose) ♥ Trauma (esp. non-accidental) ♥ Tension pneumothorax ♥ Tamponade (cardiac) ♥ Thrombus (PE)

Sinus pause



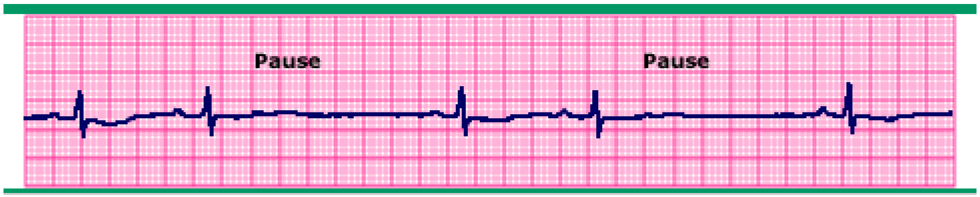
Sinus pause is the result of intermittent failure of sinus node impulse generation. This is manifest as a long RR cycle length (in this tracing P to P interval) which is longer than the RR interval of the underlying sinus rhythm. There is no relationship between the cycle length of the pause and that of the intrinsic sinus rhythm. The P-P interval for the beats before and after the pause are less than two times the underlying sinus P-P interval.

Single-lead electrocardiogram (ECG) showing lead V1 in type I (Wenckebach type) sinoatrial block



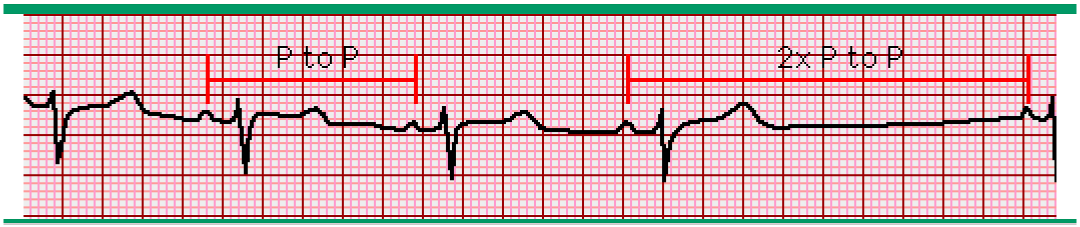
There is a 3:2 SA block, resulting in group beating of pairs of sinus beats. The P-P interval during the pause has a duration (1040 msec) that is less than two P-P cycles (1360 msec); this finding distinguishes this arrhythmia from type II SA block in which the pause duration is the same as that of two P-P cycles.

Single-lead electrocardiogram (ECG) showing lead V5 in type II sinoatrial block



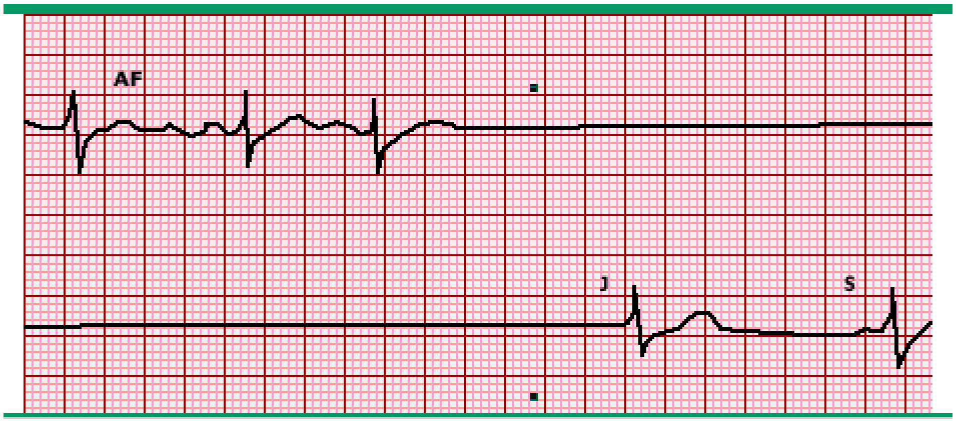
There is a 3:2 SA block, resulting in group beating of pairs of sinus beats. The P-P interval during the pause has a duration (1840 msec) that is approximately equal to two P-P cycles (920 msec); this finding distinguishes this arrhythmia from type I SA block in which the pause duration is less than that of two P-P cycles. There may be some sinus variability, as in this case, due to sinus arrhythmia and possibly to baroreceptor responses to varying diastolic filling intervals.

Sinoatrial exit block



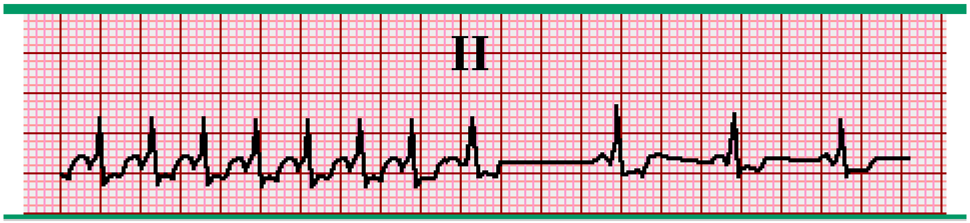
Failure of impulse conduction from the sinus node into the atrium results in sinoatrial block. This arrhythmia is characterized by an absent P wave and a prolongation of the RR cycle length (measured as P to P length in this tracing), usually twice the underlying sinus P-P interval. This is a distinguishing feature from sinus pause in which the beat after the pause has a P-P interval less than two times the underlying sinus P-P interval.

Sick sinus syndrome



Tracing of sick sinus syndrome (tachycardia-bradycardia syndrome). The initial three beats show atrial fibrillation (AF) which terminates abruptly and is followed after a long offset pause by a junctional escape beat (J) and then a sinus beat (S).

Sinus node reentry



Sinus node re-entry is due to continuous activity or re-entry within the sinus node or the sinoatrial junction. This arrhythmia has a sudden onset and offset with a rate that is usually 100 to 160 beats per minute. A P wave proceeds each QRS complex and has a morphology identical to the sinus P wave. The PR interval is also similar to that of sinus rhythm. Thus, it is only the abrupt onset and offset that distinguishes this arrhythmia from sinus tachycardia.

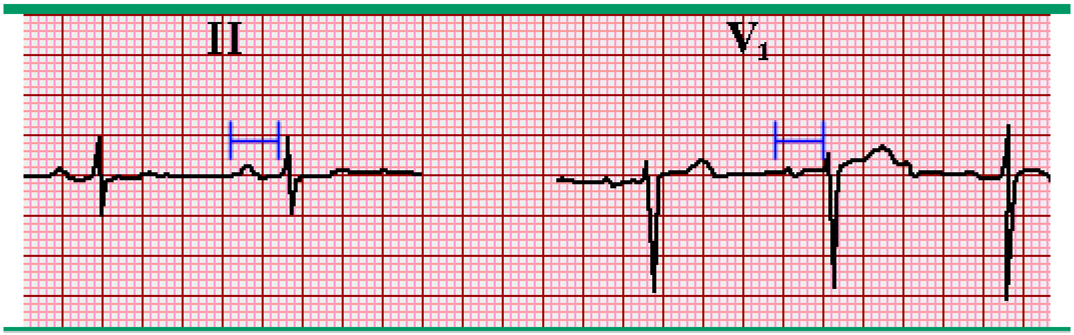
Rhythms Produced by Conduction Block

- AV Block (relatively common)
    - 1st degree AV block
    - 2nd degree AV block → type 1 and type 2
    - 3rd degree AV block
- SA Block (relatively rare)

Atrioventricular block

- Atrioventricular (AV) block may manifest as conduction delay in the AV node, intermittent failure of conduction from the atria to the ventricles, or complete AV block.

First degree atrioventricular (AV) block



First degree AV block is caused by a prolongation or delay in impulse conduction through the AV node. It is defined as a PR interval >0.20 seconds. In this case the PR interval (blue lines) is approximately 0.22 seconds.

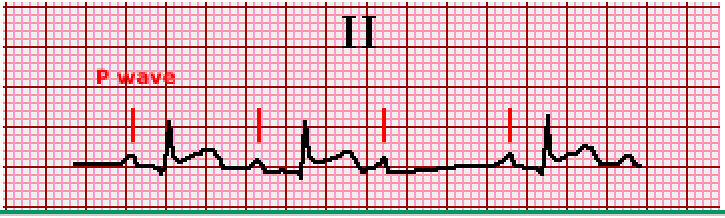
- First degree AV block, defined as a prolonged PR interval (>0.20 seconds), is not a true block but is delayed or slowed AV conduction.
- A partial list of causes of first-degree AV block include the following:
    - ✓ Underlying structural abnormalities of the node
    - ✓ An increase in vagal tone

- ✓ **MI**
- ✓ **Infiltrative CMP and DCMP**
- ✓ **Drugs** that impair or slow nodal conduction including **digoxin, beta blockers, and non-dihydropyridine CCB**
- ✓ Certain muscular dystrophies

SECOND DEGREE ATRIOVENTRICULAR BLOCK

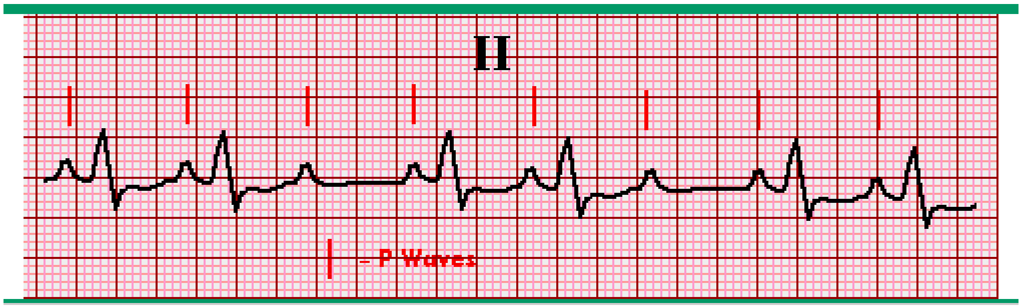
- Second degree atrioventricular (AV) block is defined as an occasional non-conducted P wave, resulting in a long RR interval.
- Second degree AV block may either be **Mobitz type I (Wenckebach) or Mobitz type II.**

Mobitz type I second degree atrioventricular (AV) block



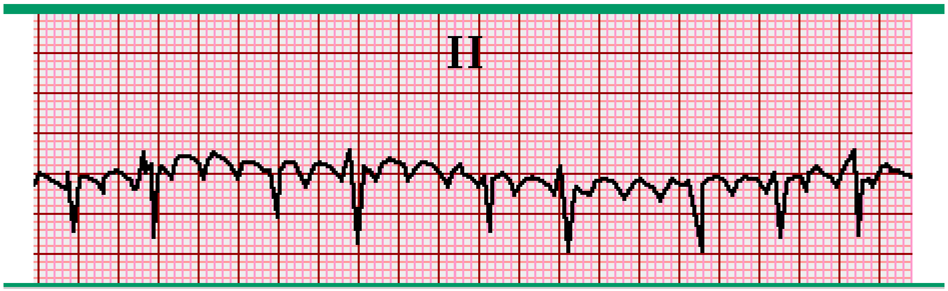
Several characteristic features of Wenckebach second degree AV block are noted on this ECG (P waves are marked by arrows): 1) The PR interval after the second P wave is longer than the preceeding PR interval; the third P wave is not conducted at all. 2) The PP intervals are constant; however, the RR interval surrounding the completely blocked P wave is longer than the preceeding normal RR interval. 3) The fourth P wave (after the blocked beat) is conducted normally; this PR interval is shorter than the PR interval that immediately preceeded the pause.

Mobitz type II second degree atrioventricular (AV) block



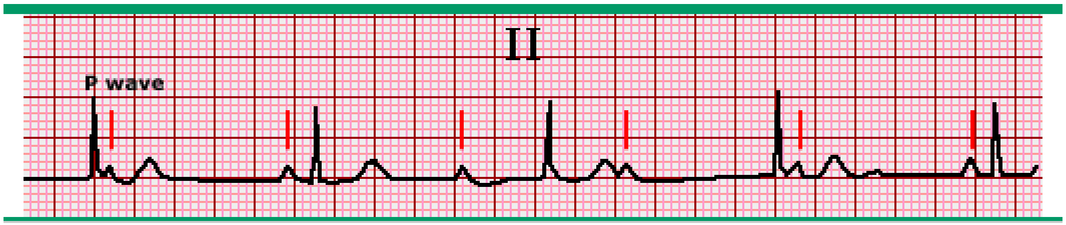
The third and sixth P waves are not conducted through the AV node (there is no associated QRS complex). The PR interval is constant prior to and after the non-conducted beats.

Variable atrioventricular (AV) block



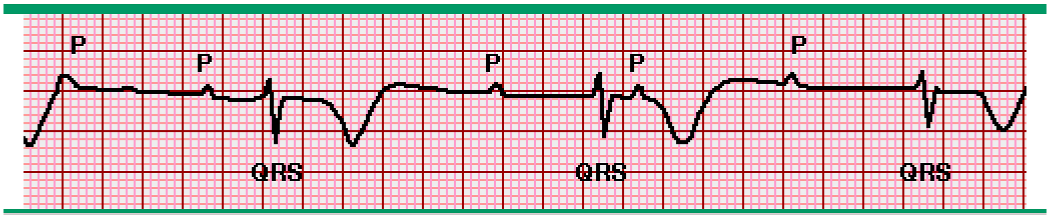
Atrial flutter is commonly associated with variable AV block. The AV conduction ratio varies between 2:1 and 3:1 in this case.

Third degree (complete) atrioventricular block with narrow QRS escape rhythm



The P waves are completely dissociated from the QRS complexes. The QRS complexes are narrow, indicating a junctional escape rhythm. The atrial and ventricular rates are stable; the former is faster than the latter.

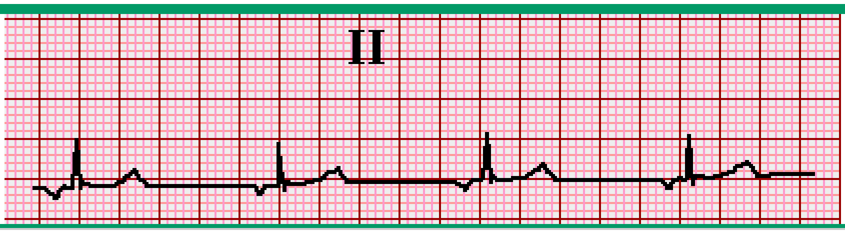
Complete heart block: Sinus rhythm with slow junctional or idioventricular escape rhythym



Multiple successive QRS complexes appear that are of ventricular origin and occur at a rate which is slower than the underlying sinus rhythm. The presence of P waves that occur independent of the QRS complexes is evidence of atrioventricular dissociation.

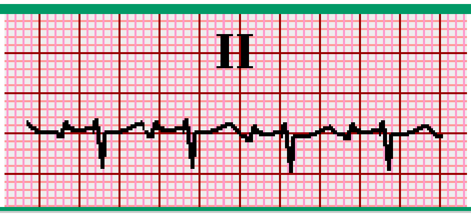
Atrial and atrioventricular nodal (supraventricular) arrhythmias

Ectopic atrial rhythm



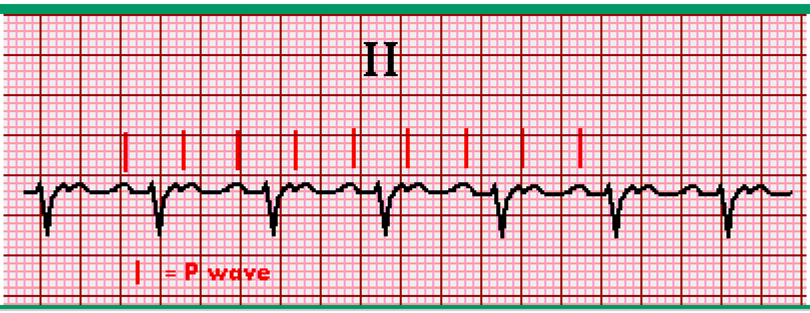
Ectopic atrial rhythm occurs when the dominant pacemaker is an ectopic focus in the atrium. The direction of atrial activation may be altered when an atrial rhythm is present since the pacemaker focus is within the atrial myocardium. In this tracing, the P wave is inverted due to retrograde atrial activation from a pacemaker focus in the low atrium, the area of the coronary sinus, or the left atrium. The QRS complexes of an atrial tachycardia resemble those seen during sinus rhythm, since myocardial activation is via the His-Purkinje system.

Atrial tachycardia



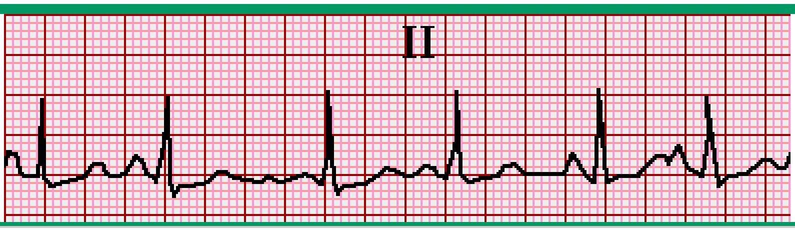
Atrial tachycardia is a supraventricular tachyarrhythmia that has a rate of 140 to 220 beats per minute. The QRS complexes occur at regular intervals (ie, there is constant RR cycle length), the P waves have a uniform morphology, and the PR interval is constant.

Atrial tachycardia with atrioventricular block



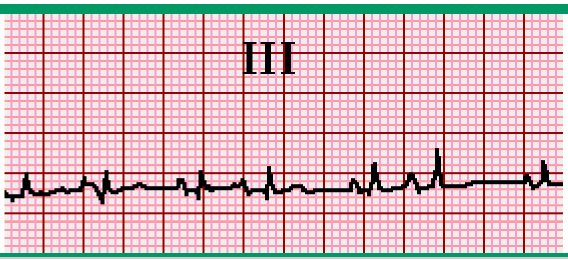
In this arrhythmia, an ectopic atrial focus is the dominant pacemaker and activates the atrial myocardium at a rate of 140 to 220 beats per minute. Due to changes in the electrophysiologic properties of the atrioventricular node, however, there is a slowing of impulse conduction through and prolongation of the refractory period of the AV node, resulting in failure of the node to conduct some of the atrial impulses. In this case, the atrial rate is 220 beats per minute and the failure to conduct occurs in a repeating 2:1 pattern.

Wandering atrial pacemaker



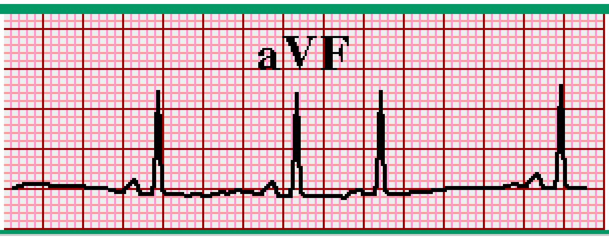
A wandering atrial pacemaker is present when there are multiple ectopic foci within the atrial myocardium that serve as dominant pacemakers. There is a changing vector of atrial activation which causes a changing P wave morphology and PR interval duration. The QRS intervals have very variable cycle lengths since the ectopic foci have differences of automaticity and rates of impulse generation. The rhythm is therefore irregularly irregular. QRS morphology is not altered from that seen during sinus rhythm, since activation of the ventricular myocardium occurs normally via the His-Purkinje system.

Multifocal atrial tachycardia



Multifocal atrial tachycardia is similar to a wandering atrial pacemaker, except that the heart rate is rapid (greater than 100 beats per minute). There is great variability of the P wave morphology and axis, the PR intervals, and the cycle lengths of the QRS complexes. The QRS complexes are unchanged and are similar to sinus rhythm since ventricular activation is normal.

Atrial premature beats



The third beat is an atrial premature beat that is normally conducted. The interval between the second sinus beat and the ectopic beat is shorter than the interval between the first two sinus beats. The P wave morphology differs from that of sinus rhythm. Since the RR cycle length is shorter, there is a decrease in the rate of conduction of the ectopic beat through the atrioventricular node. The PR interval is therefore longer than that of the sinus beat. Activation of the ventricular myocardium occurs in a normal fashion; as a result, the QRS complex is unchanged from that of sinus rhythm.

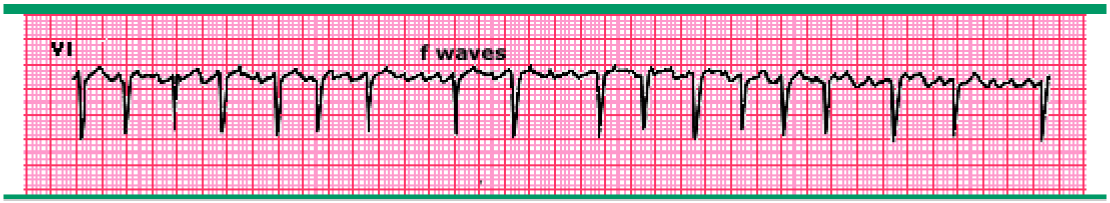
ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial Fibrillation is associated with the following changes on ECG

- **Lack of discrete P waves.**
- Fibrillatory or f waves are present at a rate that is generally between **350 and 600 beats/minute**; the f waves vary continuously in amplitude, morphology, and intervals.
- Ventricular response follows no repetitive pattern; the variability in the intervals between QRS complexes is often termed **"irregularly irregular.**"
- The ventricular rate (especially in the absence of AV nodal blocking agents or intrinsic conduction disease) usually ranges between 90 to 170 beats/min.

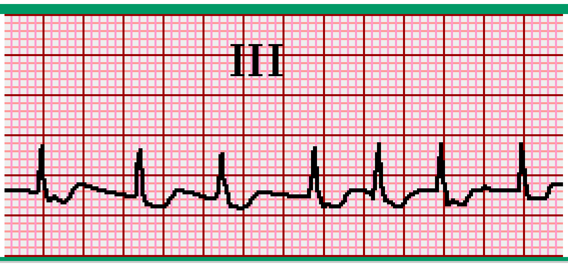
- The QRS complexes are narrow unless AV conduction through the His Purkinje system is abnormal due to functional (rate-related) aberration, pre-existing bundle branch or fascicular block, or ventricular preexcitation with conduction down the accessory pathway.

Single-lead electrocardiogram (ECG) showing atrial fibrillation



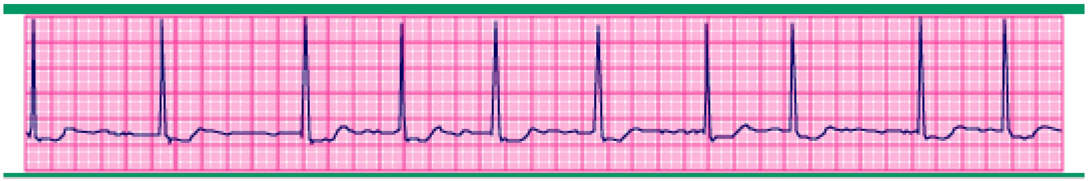
Lead V1 showing coarse AF with moderate ventricular response. The two characteristic findings in AF are present: the very rapid atrial fibrillatory waves (f waves), which are variable in appearance; and the irregularly irregular ventricular response as the R-R interval between beats is unpredictable. Coarse AF may appear similar to atrial flutter. However, the variable height and duration of the f waves differentiate them from atrial flutter (F) waves, which are identical in appearance and occur at a constant rate of about 250 to 350 beats/min.

Atrial fibrillation

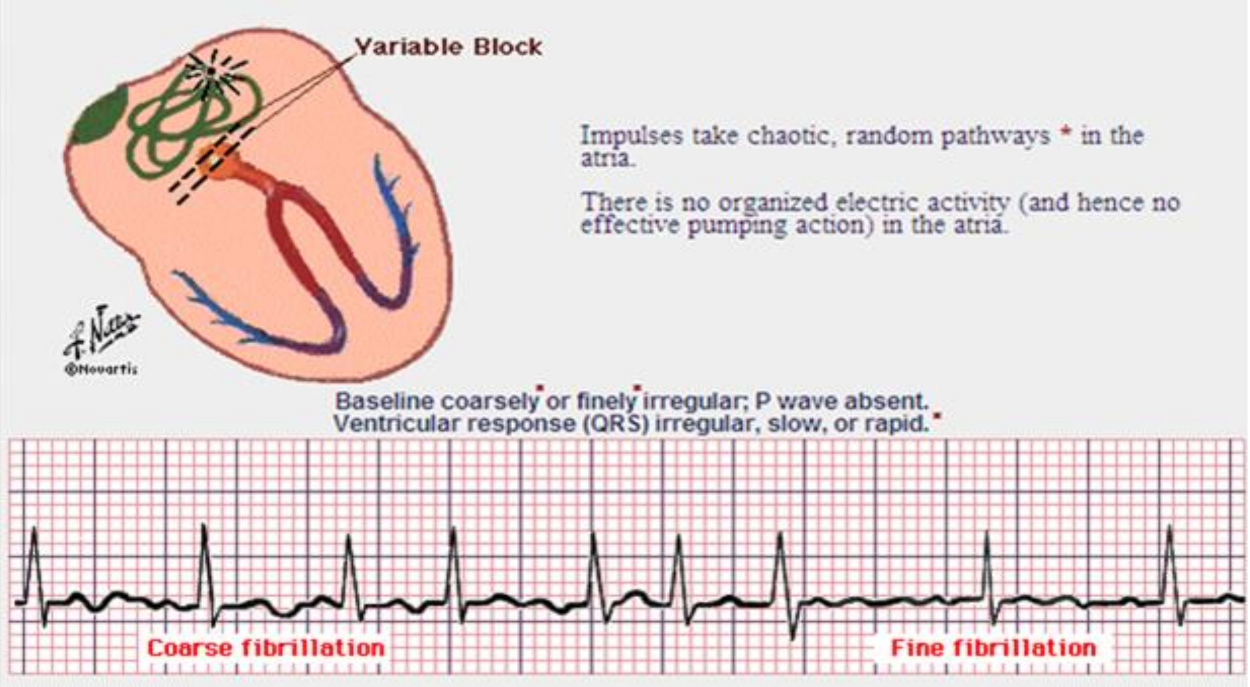


Atrial fibrillation is an irregularly irregular rhythm without regular or organized atrial activity. Atrial activation is rapid (generally greater than 320 beats per minute) and of various amplitudes. No discrete P waves are seen on this tracing. Instead, rapid, irregular, variable and low amplitude oscillating fibrillatory waves are observed between the QRS complexes. When the arrhythmia is of long duration, the fibrillatory waves may be inapparent.

Single-lead electrocardiogram (ECG) showing atrial fibrillation with minimally apparent atrial activity



F waves are not apparent in this lead, as the only finding suggestive of AF is the irregularly irrregular ventricular response.



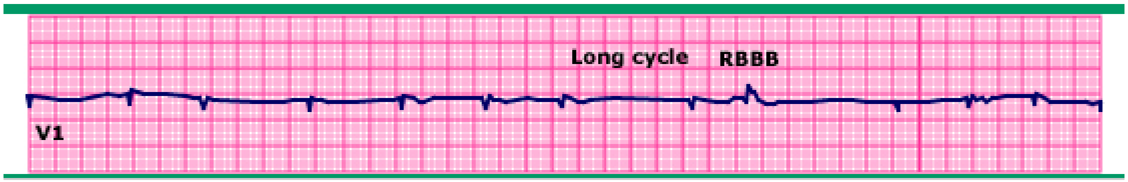
Impulses take chaotic, random pathways * in the atria.

There is no organized electric activity (and hence no effective pumping action) in the atria.

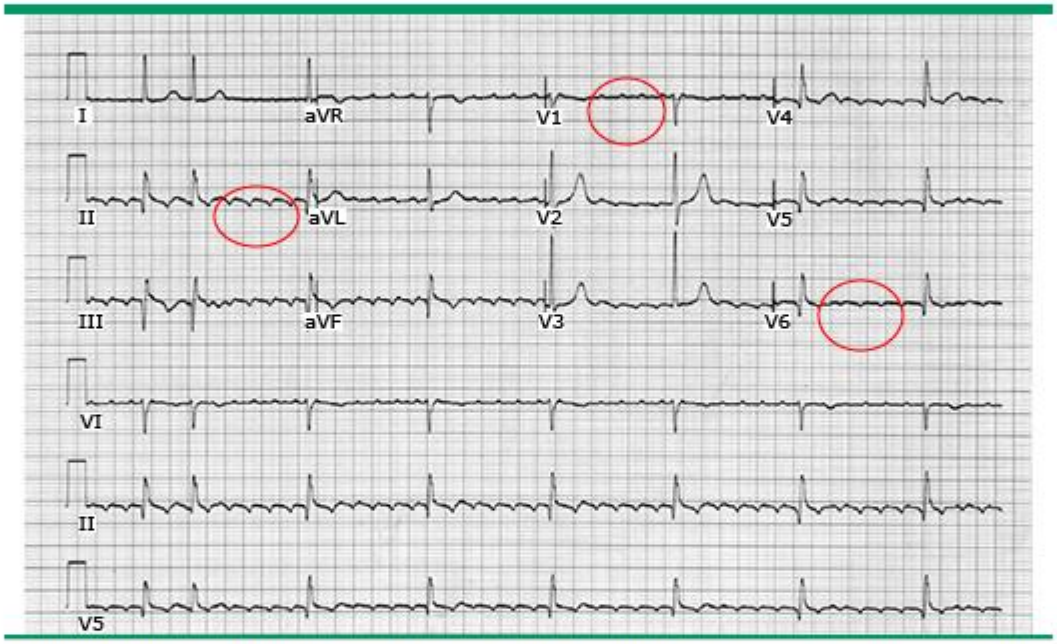
Baseline coarsely* or finely* irregular; P wave absent.
Ventricular response (QRS) irregular, slow, or rapid.*

Image; AF

Functional right bundle branch block (RBBB) in atrial fibrillation occurring in the short cycle following a preceding long cycle that lengthened the refractory period in the right bundle branch (the ashman phenomenon)



ECG of counterclockwise typical atrial flutter



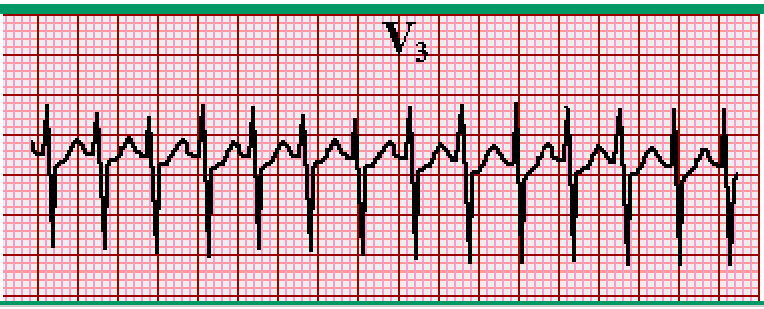
Sawtooth-like oscillations of baseline between flutter waves, best seen in the inferior leads.

* Negative flutter waves in II, III, aVF, V6. Positive flutter waves in V1.
ECG: electrocardiogram.

Ventricular arrhythmias

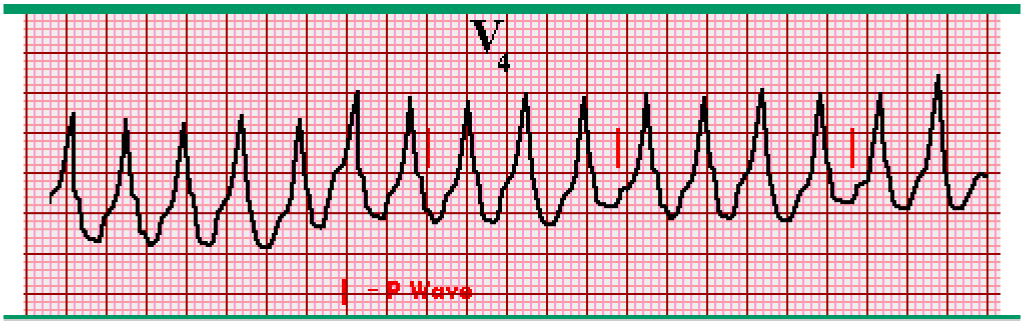
- Ventricular arrhythmias are wide complex rhythms that may be regular or irregular.
- These may be normal rate, bradycardic, or tachycardic, and may occur as single beats or sustained.
- Some ventricular arrhythmias may be present as sudden cardiac arrest.

AV nodal reentrant tachycardia



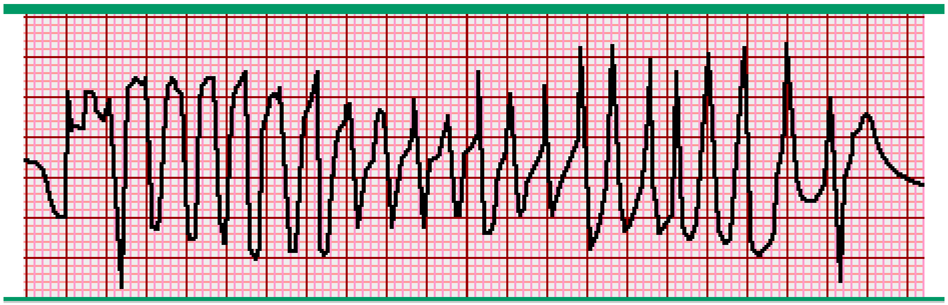
Atrioventricular nodal reentrant tachycardia is a supraventricular tachyarrhythmia that originates within the atrioventricular node. The rate is generally between 140 to 220 beats per minute and there is usually a 1:1 atrial-ventricular association; as a result, every QRS complex has an associated P wave. In this case, atrial and ventricular activation are simultaneous; as a result, the P wave is superimposed upon the QRS complex and therefore not obvious on the surface ECG.

Single lead electrocardiogram (ECG) showing monomorphic ventricular tachycardia



Three or more successive ventricular beats are defined as ventricular tachycardia (VT). This VT is monomorphic since all of the QRS complexes have an identical appearance. Although the P waves are not distinct, they can be seen altering the QRS complex and ST-T waves in an irregular fashion, indicating the absence of a relationship between the P waves and the QRS complexes (ie, AV dissociation is present).

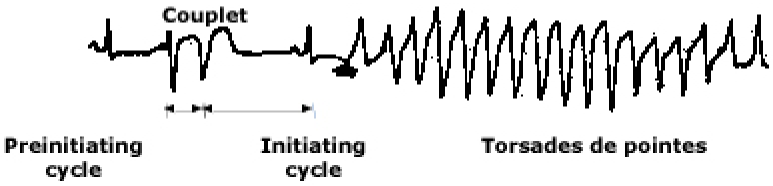
Single lead electrocardiogram (ECG) showing torsades de pointes



This is an atypical, rapid, and bizarre form of ventricular tachycardia that is characterized by a continuously changing axis of polymorphic QRS morphologies.

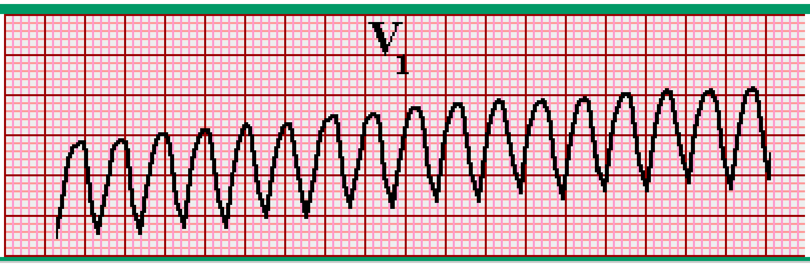
Torsade's de pointes = "twisting of points"

Single lead electrocardiogram (ECG) showing torsades de pointes



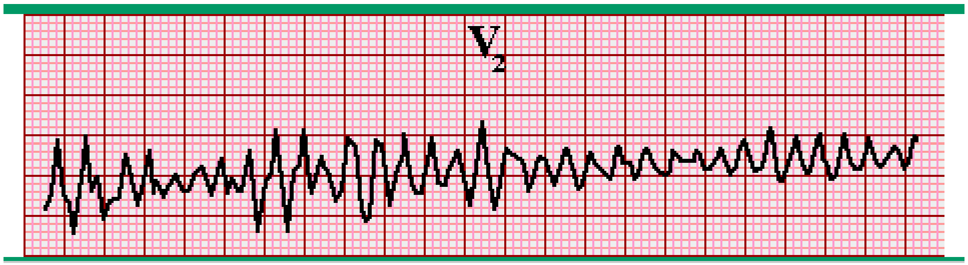
The electrocardiographic rhythm strip shows torsades de pointes, a polymorphic ventricular tachycardia associated with QT prolongation. There is a short, preinitiating RR interval due to a ventricular couplet, which is followed by a long, initiating cycle resulting from the compensatory pause after the couplet.

Ventricular flutter



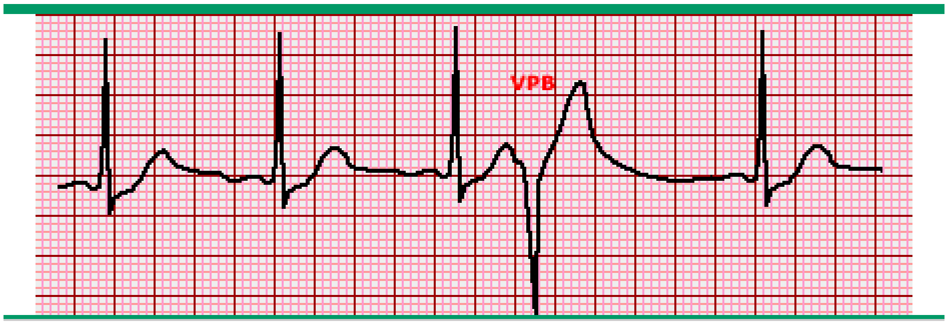
A rapid ventricular tachycardia, with rates usually over 240 beats per minute, is characteristic of ventricular flutter, with predominantly monomorphic QRS complexes, and an absence of atrial activity (P waves).

Single lead electrocardiogram (ECG) showing ventricular fibrillation



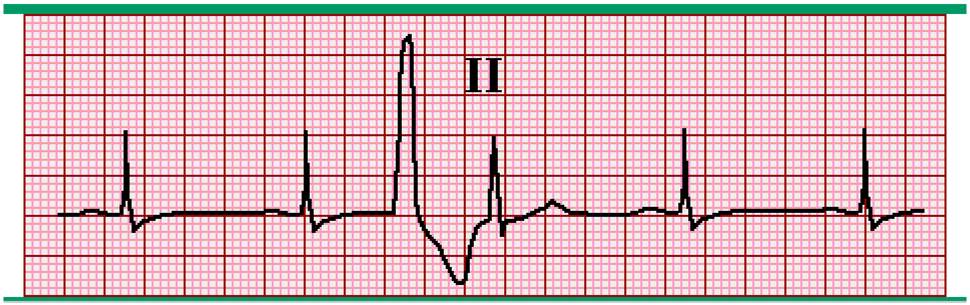
There is a complete absence of properly formed QRS complexes and no obvious P waves. A recent onset (eg, within minutes) of the arrhythmia is suggested by the coarse morphology of the fibrillatory waves.

Single lead electrocardiogram (ECG) showing a ventricular premature beat (VPB)



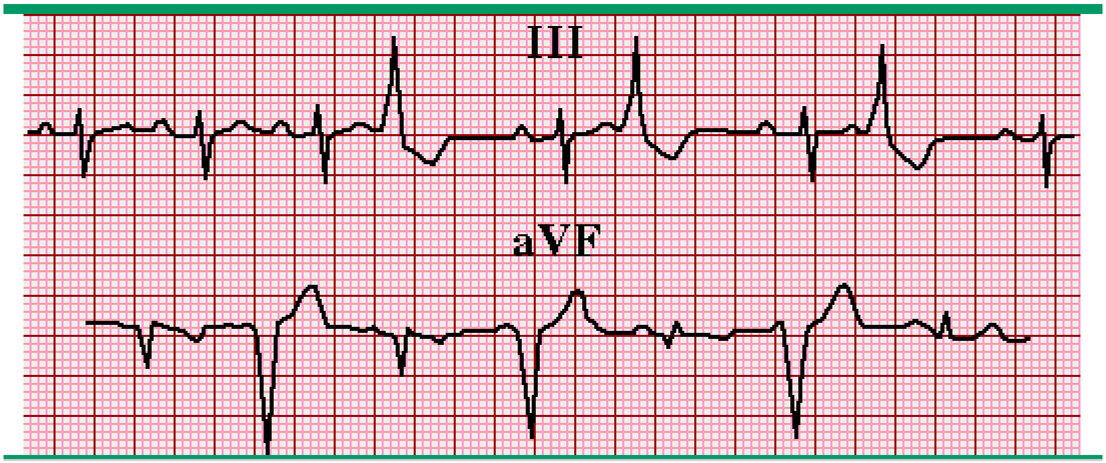
The fourth beat is a ventricular premature beat (VPB). It has a wide, bizarre morphology, with a duration >0.16 seconds.

Single lead electrocardiogram (ECG) showing an interpolated ventricular premature beat (VPB)



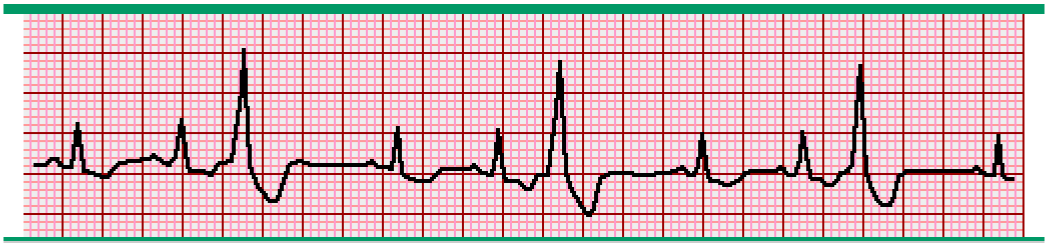
The third beat is a ventricular premature beat (VPB). It is called an interpolated VPB since it does not alter the underlying sinus RR interval.

Electrocardiogram (ECG) showing ventricular bigeminy



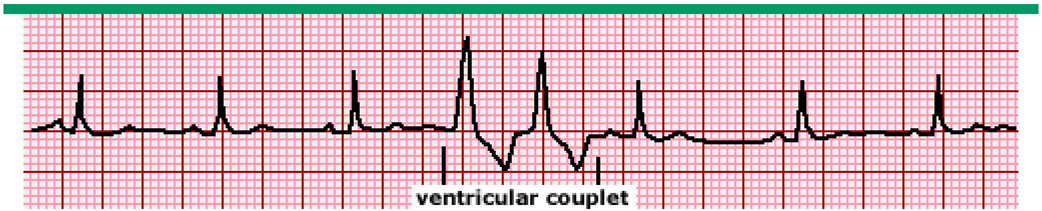
A ventricular premature beat (VPB) follows each sinus beat, and the coupling interval between the VPB and the previous sinus QRS complex is constant (fixed coupling interval). The resulting pattern is referred to as ventricular bigeminy.

Single lead electrocardiogram (ECG) showing ventricular trigeminy



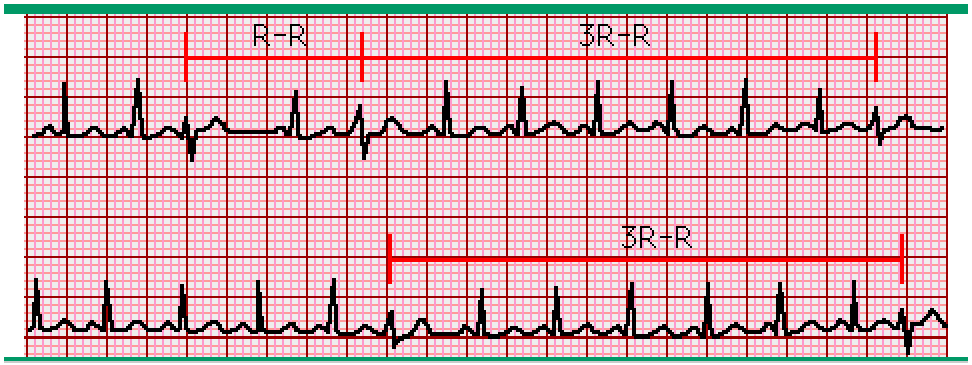
Every third beat is a ventricular premature beat (VPB). The coupling interval between the VPB and the previous sinus QRS complex is constant (fixed coupling interval). The resulting pattern is referred to as ventricular trigeminy.

Ventricular couplet



Two ventricular premature beats (VPBs) occur following three normal QRS complexes. This is a unifocal couplet since both VPBs have the same morphology.

Electrocardiogram (ECG) showing ventricular parasystole

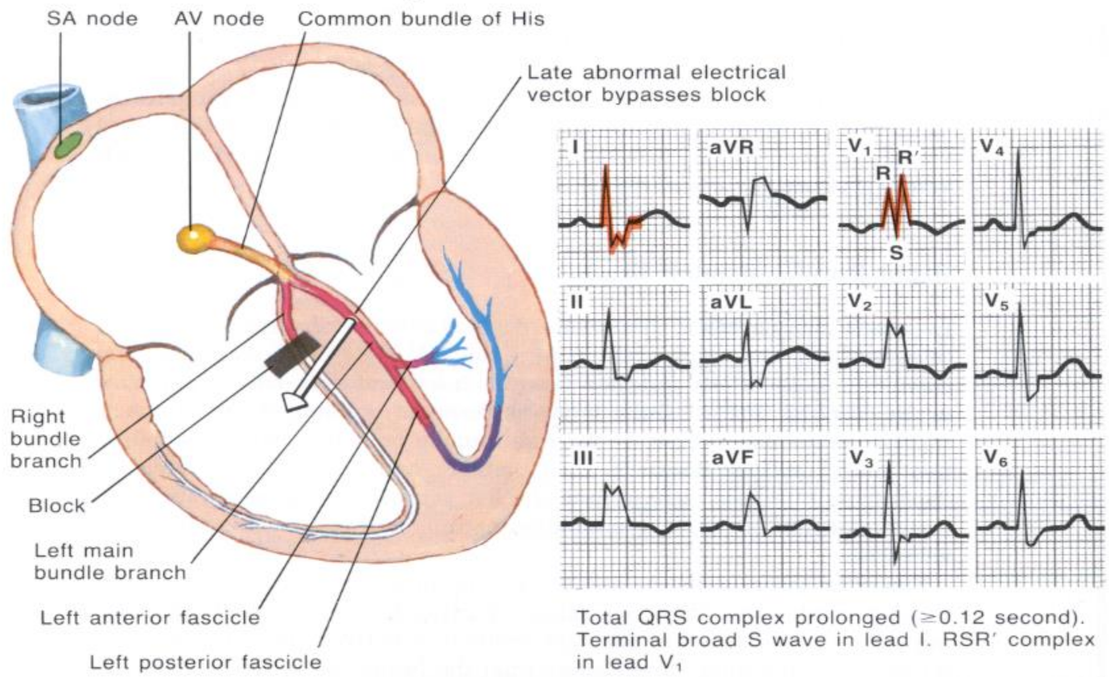


Unifocal parasystolic ventricular premature beats (VPBs) occur at a rate which is slower than the underlying sinus rhythm and manifest different coupling intervals (ie, the distance between the VPB and the prior QRS complex). The ectopic focus does not always activate the ventricular myocardium (and therefore does not produe a VPB and the ECG) since it may arrive at a time when the ventricle is refractory due to activation from the normal conduction pathway. However, the interval between two successive VPBs is always some integer of the underlying rate of the ectopic focus (the interectopic intervals have a common denominator) since the ectopic focus is undisturbed and continues to fire at its own intrinsic rate.

Intraventricular block

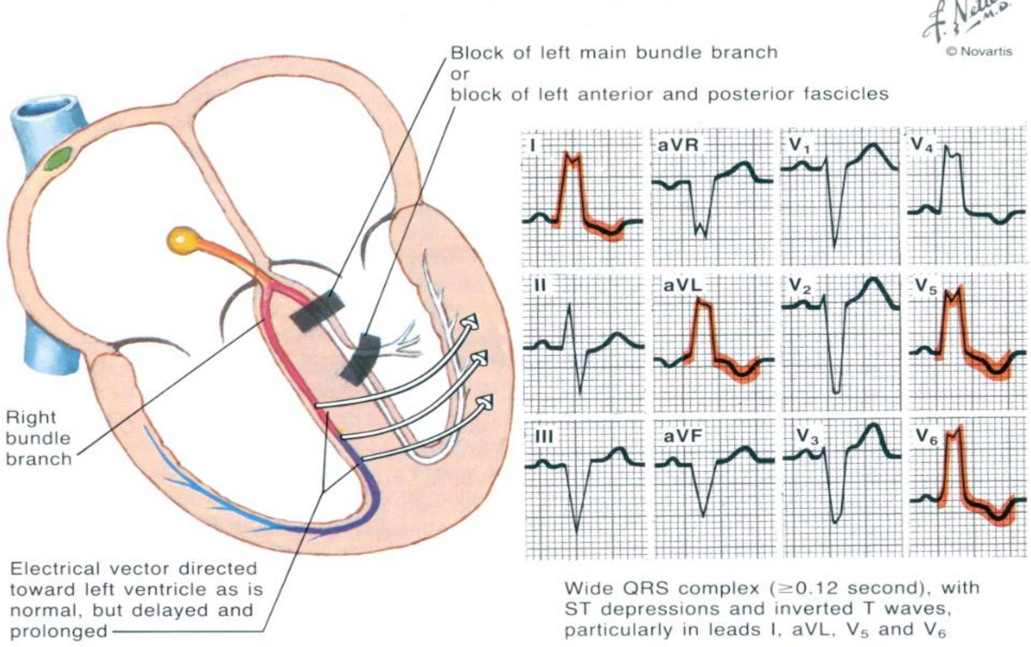
- RIGHT BUNDLE BRANCH BLOCK
  - Incomplete RBBB
  - Complete RBBB
- LEFT BUNDLE BRANCH BLOCK
  - Incomplete LBBB
  - Complete LBBB

Right Bundle Branch Block


SA node
AV node
Common bundle of His
Late abnormal electrical vector bypasses block
Right bundle branch
Block
Left main bundle branch
Left anterior fascicle
Left posterior fascicle
I
aVR
V1
R
R′
S
V4
II
aVL
V2
V5
III
aVF
V3
V6

Total QRS complex prolonged (≥0.12 second). Terminal broad S wave in lead I. RSR′ complex in lead V1

Left Bundle Branch Block

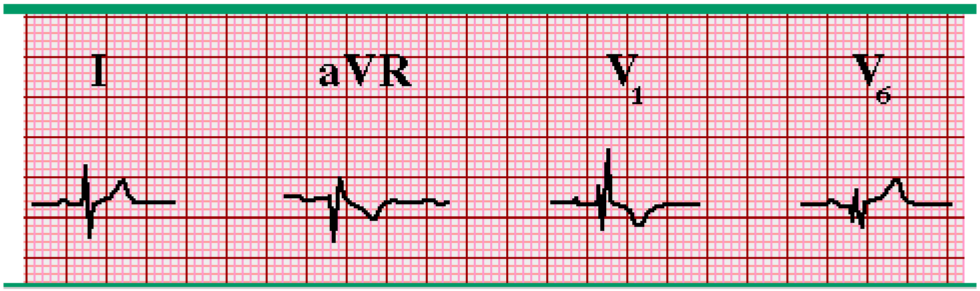

F. Netter M.D.
© Novartis
Right bundle branch
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Block of left main bundle branch or block of left anterior and posterior fascicles

Electrical vector directed toward left ventricle as is normal, but delayed and prolonged

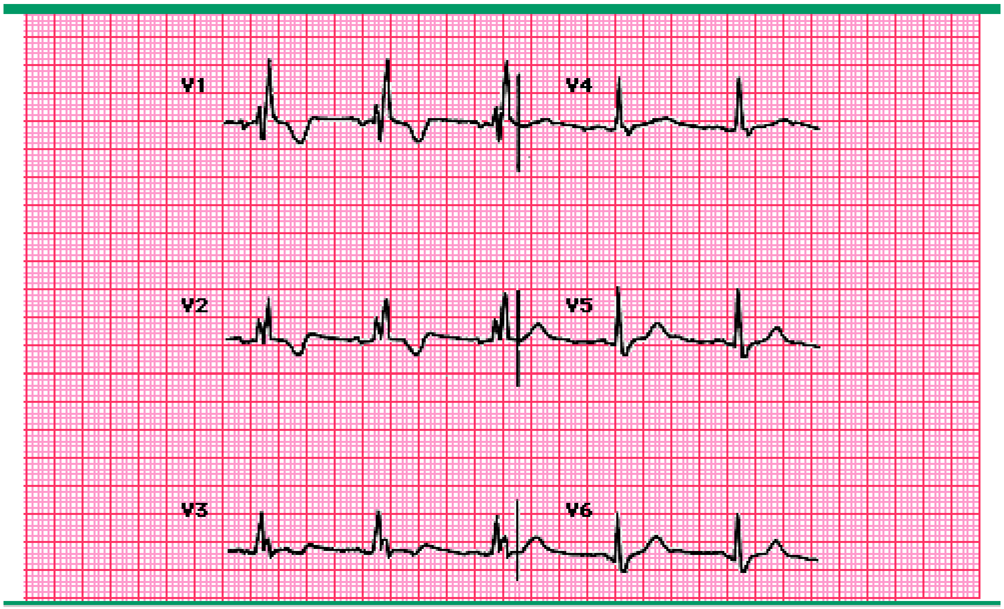
Wide QRS complex (≥0.12 second), with ST depressions and inverted T waves, particularly in leads I, aVL, V5 and V6

Incomplete right bundle branch block



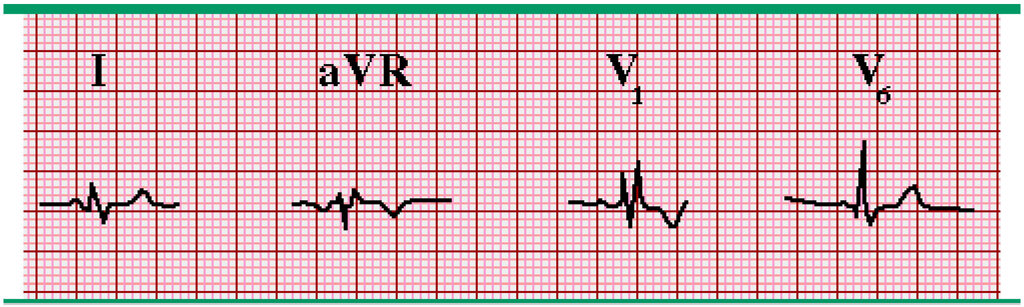
Delayed conduction through the right bundle branch does not affect the initial portion of the QRS complex (septal activation), but alters the terminal portion. There is an rsR' pattern in leads aVR and V1, and a qRs morphology in leads I and V6. The width of the QRS complex is only slightly prolonged, between 0.10 and 0.12 seconds.

Electrocardiogram (ECG) showing common right bundle branch block (RBBB)



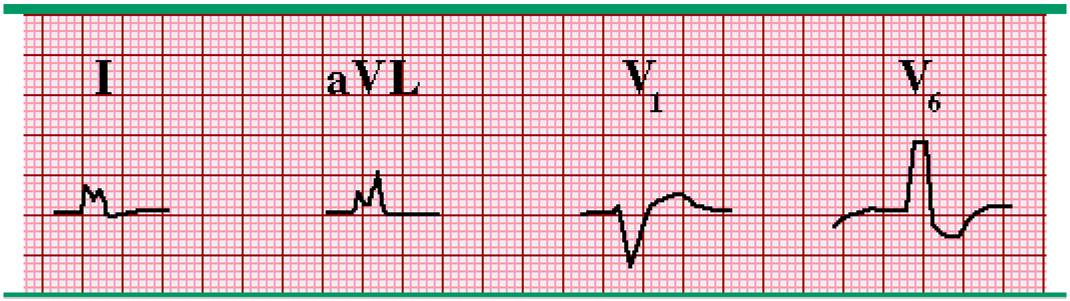
Electrocardiogram showing characteristic changes in the precordial leads in common RBBB. The asynchronous activation of the two ventricles increases the QRS duration (0.13 sec). The terminal forces are rightward and anterior due to the delayed activation of the right ventricle, resulting in an rsR' pattern in the anterior-posterior lead V1 and a wide negative S wave in the left-right lead V6 (and, not shown, in lead I).

Complete right bundle branch block



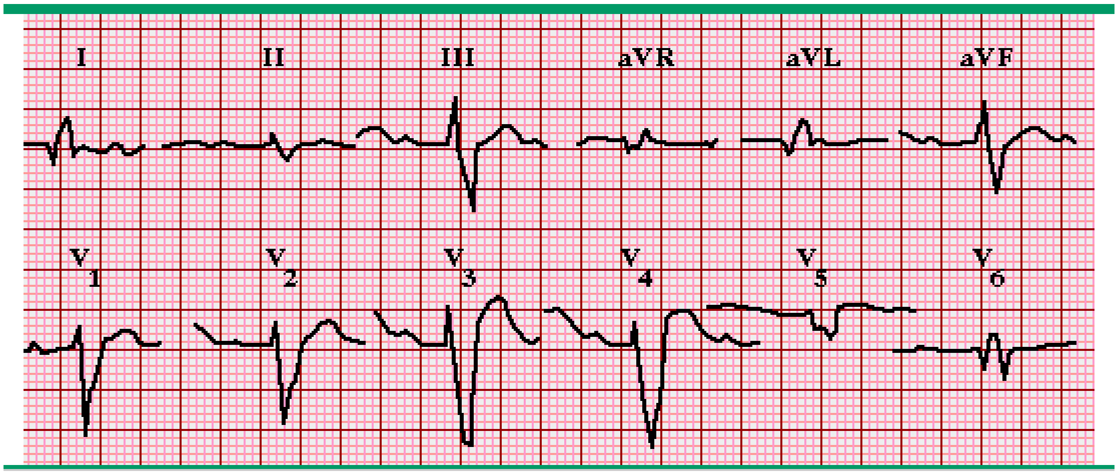
The initial myocardial activation is normal; thus, there is a normal septal q wave in leads 1 and V6, followed by a tall R wave. Similarly, there is a normal initial septal R wave followed by a deep S wave in leads aVR and V1. However, the subsequent abnormal right ventricular activation occurs from left to right and goes through the ventricular myocardium instead of the His-Purkinje system; thus, there will be a tall and broad secondary R wave (R') in leads aVR and V1 (a RSR' complex), and a deep and broad S wave in leads I and V6. The width of the QRS complex is >0.12 sec.

Complete left bundle branch block



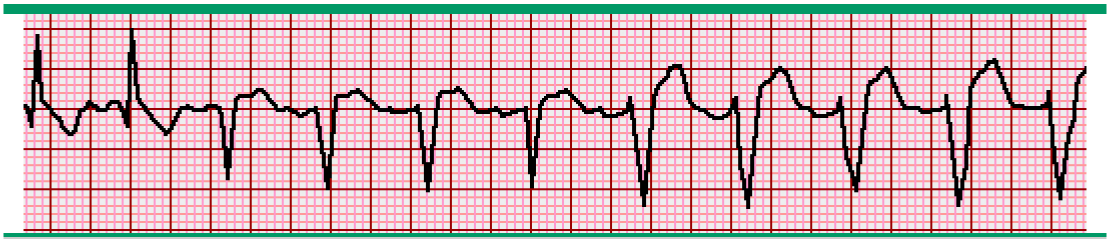
Delayed and abnormal activation of the left ventricular myocardium, and a diffuse slowing of conduction throughout the left ventricle leads to the following changes on the ECG: there is a tall monophasic and broadened R wave in leads I, aVL, and V6 instead of a septal Q wave; there is a QS complex which is abnormal and widened in V1 instead of a small initial R wave due to septal activation; the QRS interval is prolonged >0.12 seconds; myocardial repolarization changes including T wave inversion and ST segment depression are evident.

Intraventricular conduction delay


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

The QRS duration is >0.10 seconds, but the QRS morphology does not resemble a left or right bundle branch block.

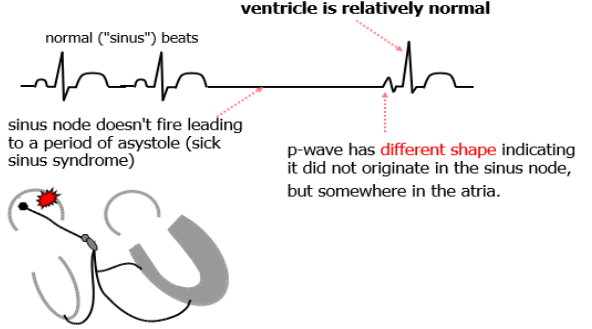
Bilateral bundle branch block



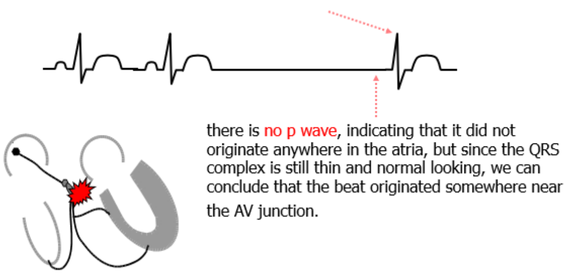
Blocked or delayed conduction in both the left and right bundle branches leads to wide QRS complexes, which in this case have coexisting complexes with a left or right bundle branch block morphology. The first two beats have the appearance of a right bundle branch block, followed by four normal beats, and then beats with the appearance of a left bundle branch block.

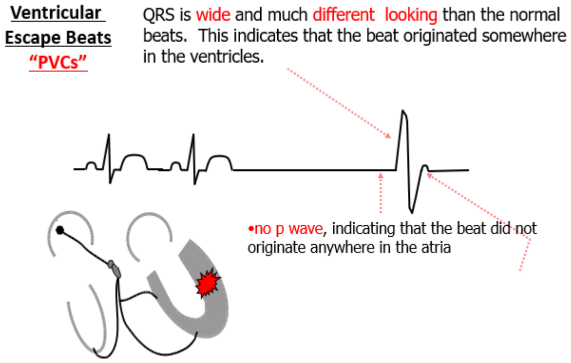
Ectopic Foci and Beats

Atrial Ectopic Beats


QRS is slightly different but still narrow, indicating that conduction through the ventricle is relatively normal
normal ("sinus") beats
sinus node doesn't fire leading to a period of asystole (sick sinus syndrome)
p-wave has different shape indicating it did not originate in the sinus node, but somewhere in the atria.

Junctional Ectopic Beats


QRS is slightly different but still narrow, indicating that conduction through the ventricle is relatively normal
there is no p wave, indicating that it did not originate anywhere in the atria, but since the QRS complex is still thin and normal looking, we can conclude that the beat originated somewhere near the AV junction.



Ventricular Escape Beats "PVCs"

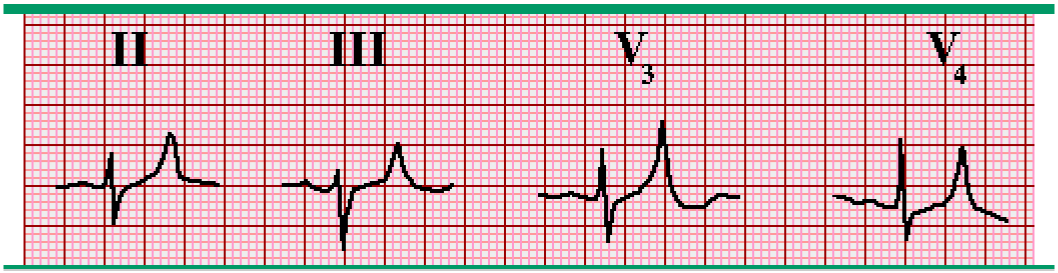
QRS is wide and much different looking than the normal beats. This indicates that the beat originated somewhere in the ventricles.

•no p wave, indicating that the beat did not originate anywhere in the atria

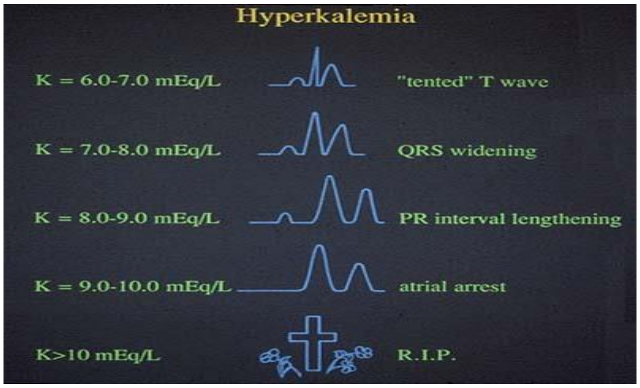
6.6.5 Electrolyte abnormalities

- Hyperkalemia
- Hypokalemia
- Hypocalcemia
- Hypercalcemia

ECG showing peaked T waves in hyperkalemia

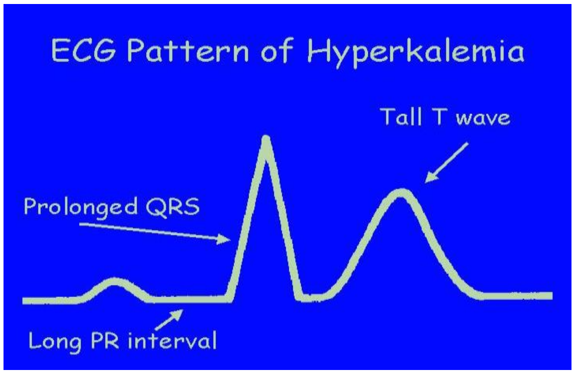


A tall peaked and symmetrical T wave is the first change seen on the electrocardiogram (ECG) in a patient with hyperkalemia.



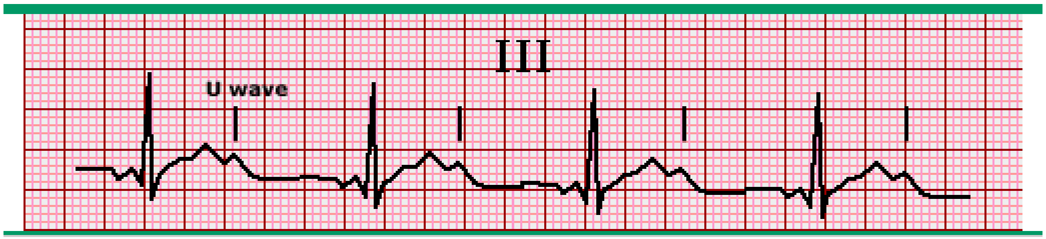
Hyperkalemia

K = 6.0-7.0 mEq/L	"tented" T wave
K = 7.0-8.0 mEq/L	QRS widening
K = 8.0-9.0 mEq/L	PR interval lengthening
K = 9.0-10.0 mEq/L	atrial arrest
K>10 mEq/L	R.I.P.

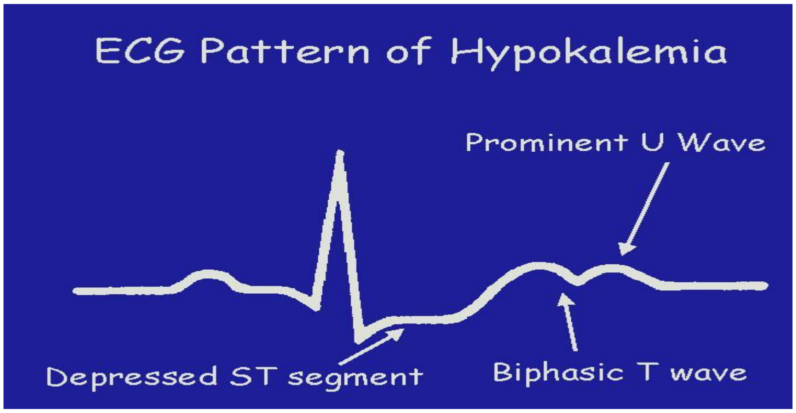


ECG Pattern of Hyperkalemia

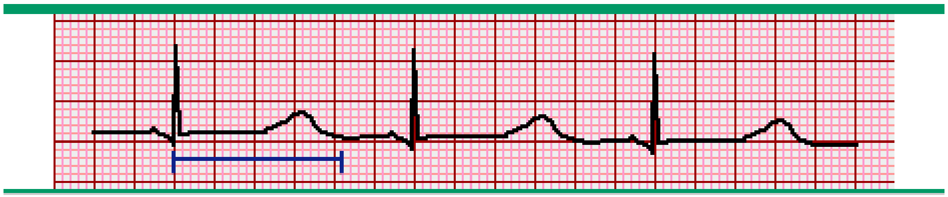
Hypokalemia



An increase in the amplitude of U waves, which occur at the end of the T wave, are characteristic of hypokalemia.

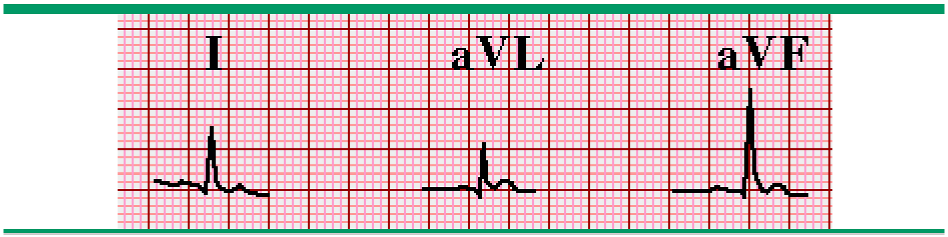

ECG Pattern of Hypokalemia
Prominent U Wave
Depressed ST segment
Biphasic T wave

Hypocalcemia



QT interval prolongation is the hallmark of hypocalcemia. In this example, the corrected QT interval is >0.6 seconds (normal ≤0.44 seconds).

Hypercalcemia



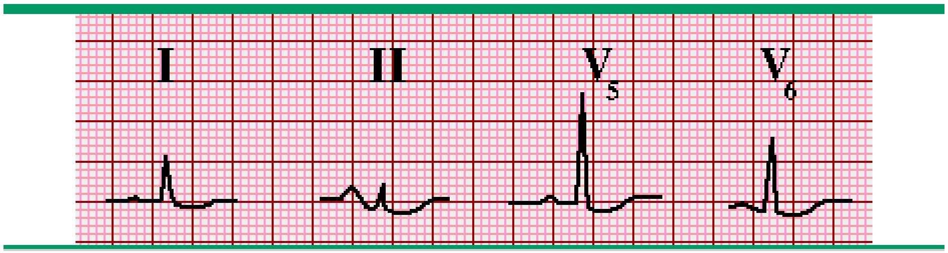
A short QT interval (<0.36 seconds), primarily secondary to a decrease in the ST segment duration, is characteristic of hypercalcemia. The initial portion of the T wave has an abrupt upslope.

6.6.6 Drug toxicity

Digoxin and digitoxin toxicity

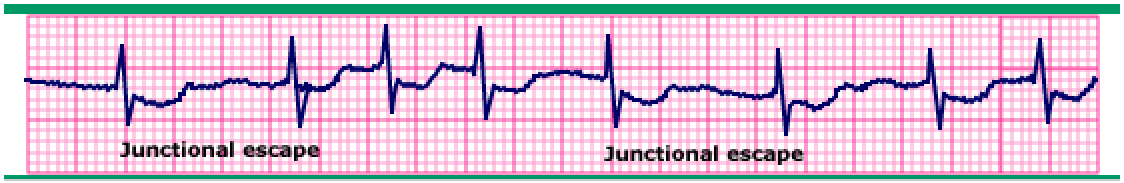
- ECG features of hyperkalaemia, sinus bradycardia, sinoatrial arrest, and 2nd or 3rd degree AV block are common.

Digitalis effect



The ST segment is depressed and concave upward.

Single-lead electrocardiogram (ECG) showing atrial fibrillation (AF) with junctional escape beats suggesting digoxin toxicity



The 4 electrocardiograms in this sequence demonstrate increasing severity of digoxin toxicity in a patient with atrial fibrillation.
This ECG shows atrial fibrillation with an irregularly irregular ventricular response. However, the longest recurring R-R intervals are constant, suggesting junctional escape beats due to AV nodal block. The escape interval of 680 msec indicates an accelerated automatic pacemaker with a rate of 88 beats/min.

Phenytoin toxicity

- ✓ ECG -reveals increased PR interval, widened QRS interval, and altered ST segments and T waves, arrhythmias, ventricular tachycardia, primary ventricular fibrillation, atrioventricular block, or sinus arrest with junctional or ventricular escape that may occur after intravenous (or very rarely oral) exposure

Phenothiazine toxicity

- ✓ ECG → usually shows QT interval prolongation and occasionally QRS prolongation (particularly with thioridazine and Risperidone).

Chapter 7; Basics about rational use of antibiotics

Dr. Mulualem. G

- WHO defines the rational use of antibiotics as the correct, proper and appropriate use of antibiotics.
- Rational use of antibiotics requires that the patient receives medications appropriate to their clinical needs in doses that meet their own individual requirements for an adequate period of time and lowest cost to them and their community.
- Antibiotics can be used as: Prophylaxis, Empirical or Definitive treatment

6.6.6.1 Dosing and common terminologies

- ''Stat'' means given as a ''single dose'' only and there is no any other repeat dose. E.g. Albendazole, 400mg, PO, stat
- QD (lat. Quaque in die) = daily, once per day, every 24 hours (q 24hr)
  - Don't use the term ''QD'', because the pharmacist may misinterpret as ''QID''
- BID (lat. bis in die) = two times per day, every 12 hrs (2X/day or q12hr)
- TID (lat. ter in die) = three times per day, every 8 hrs (3X/day or q8hr)
- QID (lat. Quarter in die) = four times per day, every 6 hr (4X/day or q6hr)
- Dose more than 4x/day can be prescribed as → q4hr (6x/day), q3hr (8x/day), q1hr, q5min….
- Suppository → drugs to be given per rectum. E.g. PCM suppository, bisacodyl suppository
- Pessary → drugs to be inserted through vagina. E.g. clotrimazole vaginal pessary

Divided dose examples

- PTU, 300mg, PO, in 3 divided dose means 100mg, PO, TID = 300mg per day (but it doesn't mean 300mg TID)
- Ceftriaxone 2g, IV, in two divided doses = Ceftriaxone 1g, IV, BID

Loading dose and maintenance dose

- Loading is the initial and highest dose to be given once, which is followed by maintenance dose as daily, BID and the like.
- Example
  - Aspirin (ASA), 325 mg, PO, loading followed by 81mg, Po, daily
  - UFH, 5,000 IU, IV, loading then 250 IU/kg/dose, Sc, BID
  - Mannitol Loading dose 1g/kg over 30-60min, followed by a maintenance dose of 0.5g/kg every 4-6hrs

Escalation and de-escalation

- Escalation is increasing the dose progressively with some form of scale until target is achieved. The reverse is true for de-escalation
- Example
  - Refer dopamine drip preparation from shock management (click here → Shock)
  - Lisinopril 5 mg daily, escalate dose up to 40 mg Po daily if BP is uncontrolled. Which means 5mg → 10 mg → 20mg → 25mg …. Maximum limit is 40 mg
  - Amlodipine 5 mg daily, escalate to 10 mg if BP is uncontrolled.

Tapering dose

- Drugs to be tapered are those not to be stopped abruptly, rather you have to discontinue the drug by decreasing the dose gradually. By how much to be tapered depends on your target and patient's clinical response
- Example
  - Prednisone, 1-2 mg/kg/day, PO, daily or BID, for 4-6 wks, followed by gradual tapering.

Maximum daily dose

- Drugs can be given or written in ranges. So, maximum daily dose is the highest total dose to be given per day. Taking the drug above the maximum level may cause toxicity or intolerable side effects.
- Example
  - **PCM**, 500mg to 1g PRN; max 4g/day → in this case the patient can take a total of up to 4g/day (i.e 500mg 8x/day or 1g 4x/day is the maximum limit)
  - **Enalapril for hypertension;** Initial: 5 mg, PO, daily (2.5 mg, PO, daily in patients taking diuretics); titrate upward, usually at 1- to 2-week intervals; usual dose range: 10 to 40 mg daily. Target dose: 20 mg daily in 1 or 2 divided doses. **Maximum: 40 mg/day**.

6.6.6.2 Common scenarios in syrup and per body weight (per Kg) dosing

6.7 If a drug is prescribed as per day form (''x''mg/kg/day), you have to divide the final calculated amount to the frequency of dose (i.e divide by 2 for BID dose, divide by 3 for TID dose)

6.8 But, if a drug is prescribed as per dose form (''x''mg/kg/dose), you have to give the total calculated amount per each dose (frequency of dose).

6.9 Per dose and per day have no effect on once daily dosage forms

6.10 Examples

- Gentamycin, 5mg/kg/day, IV, TID, for 3 weeks is the same as gentamycin 5mg/kg/day, in three divided doses, IV, for 3 weeks

        - For example, in 60 Kg pt, 5mg/kg/day = 5 x 60kg/day = 300mg/day. 300 ÷ 3 = 100mg. So, the final prescription is gentamycin, 100mg, IV, TID
    - But, metronidazole 7.5mg/kg/dose, IV, TID is quite different from metronidazole 7.5mg/kg/day, IV, in three divided doses
        - For example, in 1o Kg pt, 7.5mg/kg/dose = 7.5 x 10Kg/dose = 75mg/dose. So, the final prescription is metronidazole, 75mg, IV, TID

How to calculate and prescribe syrup?

Let's see with amoxicillin syrup in 30 kg child

6.11 Amoxicillin syrup is available as 250mg/5ml or 125mg/5ml
6.12 If the dose of amoxicillin is 50mg/kg/day, TID, based on the above explanation 50mg/kg/day = 50mg x 30kg/day = 1500mg. since it is per day dose, we will devide for 3 (i.e. for TID dose). 1500mg/day ÷ 3 = 500mg, TID
6.13 Our target is how much ml does the child takes per each dose?
6.14 In 250mg/5ml preparation, 250mg = 5ml
500mg = x
6.15 $X = \frac{500mg\ x\ 5ml}{250mg}$ = 10ml
6.16 So, the final prescription will be, Amoxicillin syrup (250mg/5ml), 10ml, po, TID for 7 days
6.16.1 N.B one Tea spoon (tsp) = 5ml
6.17 For final dispense of this dose (for pharmacist),
6.17.1 this child needs 10ml, TID in each day which means S/he needs 10ml x 3 = 30 ml per day. The prescription is for 7 days, so 30ml/day for 7 days = 30ml x 7 = 210ml.
6.17.2 if each bottle of amoxicillin syrup contains 100ml, for 210 ml, the pharmacist should give 2 bottles of syrup (210ml ≅ 200ml).

Recommendations to avoid Poor prescription writing

6.18 generic name is preferred
6.19 ".1" is easily misread as "1," a tenfold overdose
6.20 "1.0 mg" is easily misread as "10 mg," whereas "1 mg" is not
6.21 The slash ("/") was traditionally used as a substitute for a decimal point. This should be abandoned because it is too easily misread as the numeral "1."
6.22 "10U" is easily misread as "100"; the word "units" should *always* be written out.
6.23 ''IU'' to mean International unit easily misread as IV (intravenous)
6.24 micrograms should *always* have this unit written

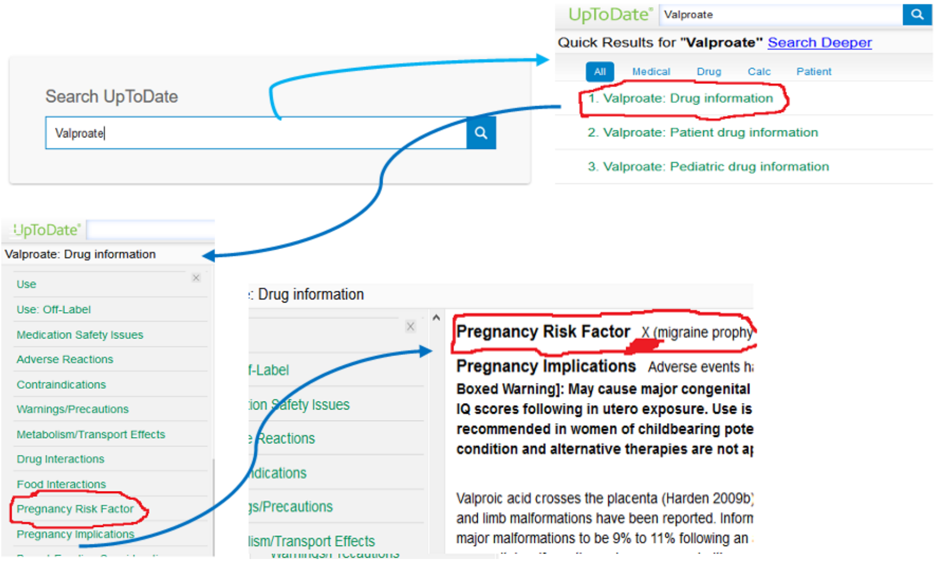
Lines of therapy

- **Difference between 1st line, 2nd line, 3rd line and alternative**

6.25 Treatment options can often be ranked or prioritized as 1st line, 2nd line, 3rd line and so on.

1st line	- It is the first therapy that will be tried - Its priority over other options is usually due to - Recommended previously based on clinical trial on efficacy, safety and tolerability - Chosen based on clinical experience of physicians (experts of the subject) - Availability and cost effectiveness especially for low income countries
2nd line	- 2nd line therapy may be substituted or added to the treatment regimen if 1st line therapy; - Fails to resolve the issue (i.e. if there is no clinical response to 1st line treatment) - Produces intolerable side effects (including allergic reaction and complications)
3rd line	➢ Reserved for microbiologic data proven resistance for 1st and 2nd line options ➢ May be substituted or added over to 2nd line if clinical response is not achieved. 2nd line therapy maybe totally substituted with 3rd line, if intolerable side effect develops.
Alternative	- This are drugs which may be less effective than the preferred drug. They are considered if the preferred drug is not available, route of administration is unavailable, too costly for the patient, or allergy to 1st line drugs etc.

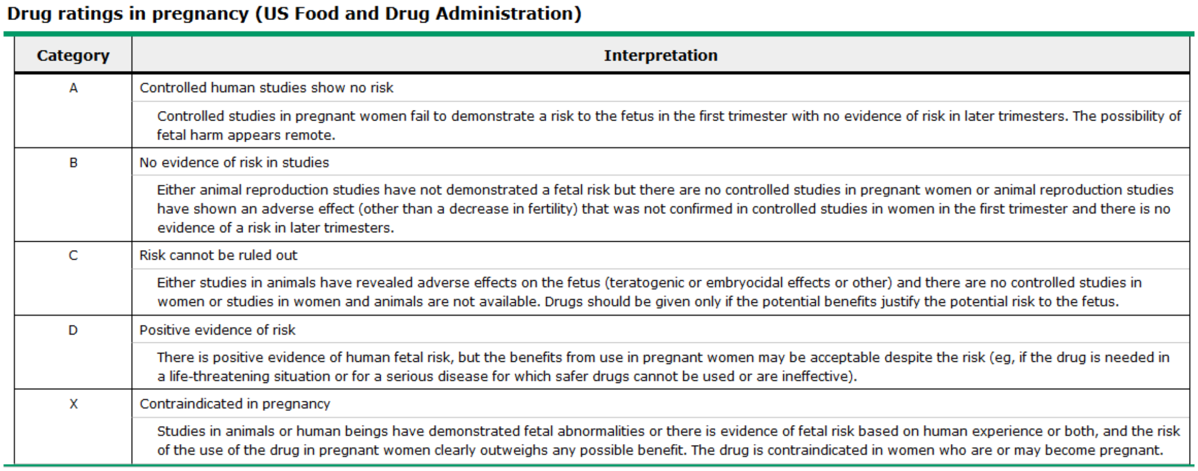
Category of drugs for pregnancy


UpToDate
Valproate
Quick Results for "Valproate" Search Deeper
All
Medical
Drug
Calc
Patient
1. Valproate: Drug information
2. Valproate: Patient drug information
3. Valproate: Pediatric drug information
Search UpToDate
Valproate
UpToDate
Valproate: Drug information
Use
Use: Off-Label
Medication Safety Issues
Adverse Reactions
Contraindications
Warnings/Precautions
Metabolism/Transport Effects
Drug Interactions
Food Interactions
Pregnancy Risk Factor
Pregnancy Implications
: Drug information
f-Label
ion Safety Issues
e Reactions
ndications
gs/Precautions
lism/Transport Effects
Pregnancy Risk Factor X (migraine prophy
Pregnancy Implications Adverse events h
Boxed Warning]: May cause major congenital
IQ scores following in utero exposure. Use is
recommended in women of childbearing pote
condition and alternative therapies are not a
Valproic acid crosses the placenta (Harden 2009b)
and limb malformations have been reported. Inform
major malformations to be 9% to 11% following an

Picture; diagrammatic example on, how to search **pregnancy risk factor of a specific drug from UpToDate**

Our (Authors) recommendation for pregnancy category drug prescription

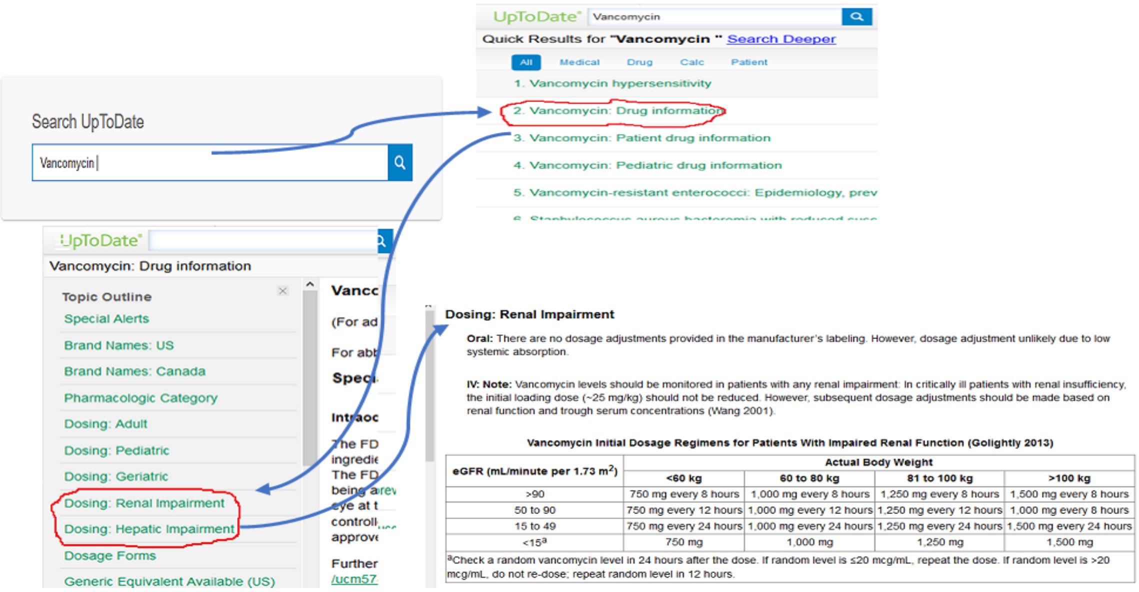
- Category A and B → prescribe safely
- Category C → Give only if the potential benefits are more necessary than the potential risk to the fetus. Otherwise, it is better to restrict these drugs during pregnancy.
- Avoid category D and X → category D can be given if there is emergency condition of the mother and the drug is lifesaving with lack of other safe drug options. Category X is absolutely contra indicated
- Look at the description below



Drug ratings in pregnancy (US Food and Drug Administration)

Category	Interpretation
A	Controlled human studies show no risk Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	No evidence of risk in studies Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Risk cannot be ruled out Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	Positive evidence of risk There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Contraindicated in pregnancy Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Dose adjustment of antibiotics in renal impairment (AKI/CKD pt') or hepatic impairment (e.g CLD pt')



Quick Results for "Vancomycin " Search Deeper

1. Vancomycin hypersensitivity
2. Vancomycin: Drug information
3. Vancomycin: Patient drug information
4. Vancomycin: Pediatric drug information
5. Vancomycin-resistant enterococci: Epidemiology, prev

Vancomycin: Drug information

- Special Alerts
- Brand Names: US
- Brand Names: Canada
- Pharmacologic Category
- Dosing: Adult
- Dosing: Pediatric
- Dosing: Geriatric
- Dosing: Renal Impairment
- Dosing: Hepatic Impairment
- Dosage Forms
- Generic Equivalent Available (US)

Dosing: Renal Impairment

Oral: There are no dosage adjustments provided in the manufacturer's labeling. However, dosage adjustment unlikely due to low systemic absorption.

IV: Note: Vancomycin levels should be monitored in patients with any renal impairment: In critically ill patients with renal insufficiency, the initial loading dose (~25 mg/kg) should not be reduced. However, subsequent dosage adjustments should be made based on renal function and trough serum concentrations (Wang 2001).

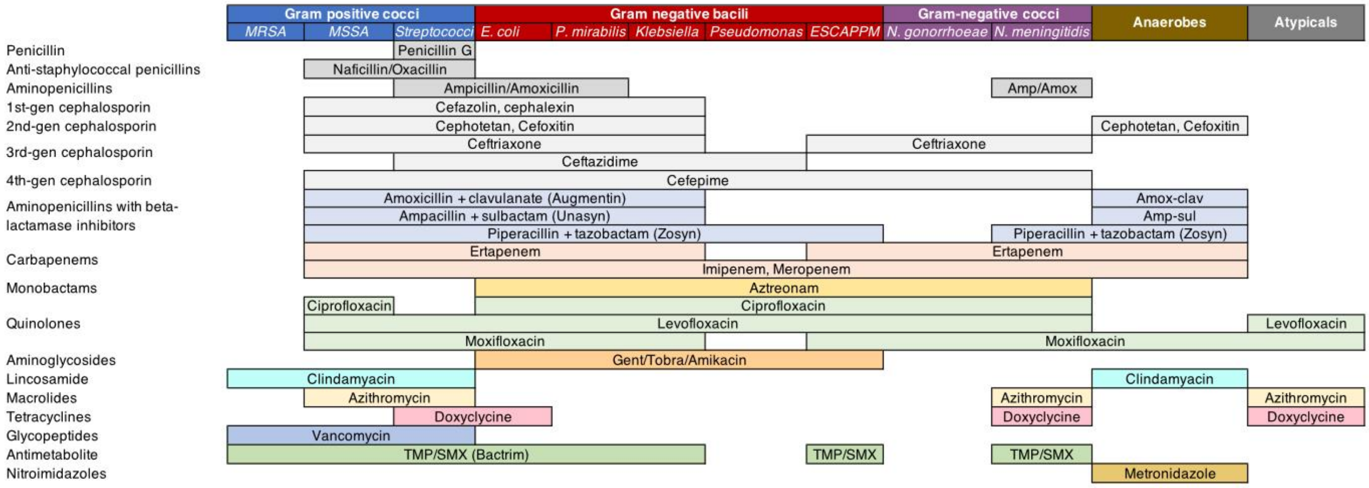
Vancomycin Initial Dosage Regimens for Patients With Impaired Renal Function (Golightly 2013)

eGFR (mL/minute per 1.73 m^2)	Actual Body Weight			
	<60 kg	60 to 80 kg	81 to 100 kg	>100 kg
>90	750 mg every 8 hours	1,000 mg every 8 hours	1,250 mg every 8 hours	1,500 mg every 8 hours
50 to 90	750 mg every 12 hours	1,000 mg every 12 hours	1,250 mg every 12 hours	1,000 mg every 8 hours
15 to 49	750 mg every 24 hours	1,000 mg every 24 hours	1,250 mg every 24 hours	1,500 mg every 24 hours
<15[a]	750 mg	1,000 mg	1,250 mg	1,500 mg

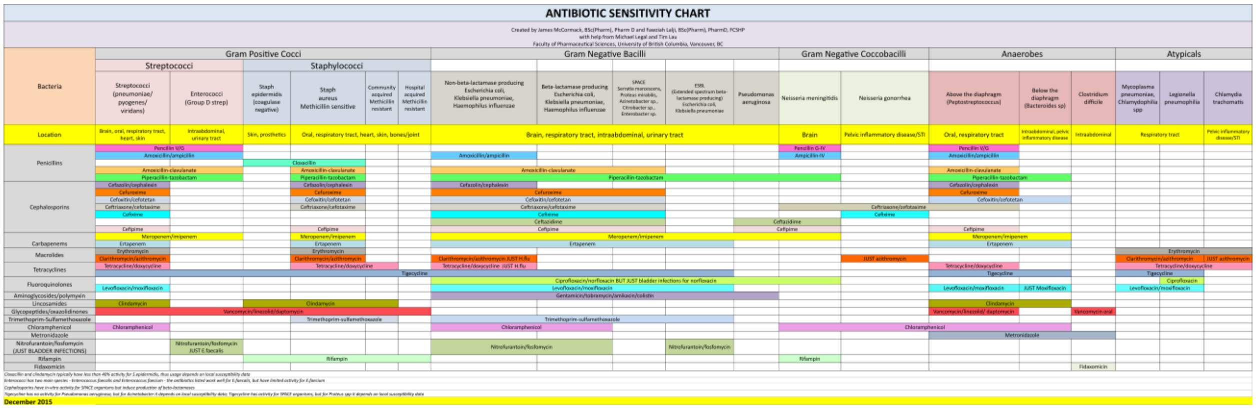
[a] Check a random vancomycin level in 24 hours after the dose. If random level is ≤20 mcg/mL, repeat the dose. If random level is >20 mcg/mL, do not re-dose; repeat random level in 12 hours.

Picture; diagrammatic example on, how to search, **a specific drug dose adjustment for renal or hepatic impairment, from UpToDate**

Antibiotic sensitivity chart



See github.com/aetherist/antibiogram for details. For educational purposes only. TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.



ANTIBIOTIC SENSITIVITY CHART

Created by James McCormack, BSc(Pharm), Pharm D and Fawziah Lalji, BSc(Pharm), PharmD, FCSHP
with help from Michael Legal and Tim Lau
Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC

December 2015

Classification of antibiotics

6.26 There are four major classes of antibiotics

- Cell wall Synthesis inhibitors
- Protein synthesis inhibitors
- Nucleic acid synthesis Inhibitors
  - Folate antagonists
  - Direct enzyme inhibitors
- Miscellaneous

Table; classes of antibiotics with common examples				
Cell wall synthesis inhibitors				
			Examples#	Antibacterial spectrum of coverage*
Beta lactam antibiotics	Penicillin	Natural penicillin	**Pen.G, Pen.V**	Streptococci, Pepto streptococcus, Intravenous Pen.G for N. Meningitidis
		Anti-staphylococcal (penicillinase resistant)	**Cloxacillin,** Oxacillin, methicillin, naficillin	MSSA, CoNS
		Amino penicillin's	**Amoxicillin, Ampicillin**	Streptococci, E. coli, klebsiella, H. influenza, Ampicillin (IV) for N.meningitidis, Pepto streptococcus
		Amino penicillin's with Beta lactamase inhibitors	Amoxicillin + clavulanic acid (**Augmentin), Ampicillin + sulbactam**	Streptococci, MSSA, G -ve bacilli except pseudomonas, Pepto streptococcus
		Extended spectrum antibiotics (Antipseudomonal)	**Piperacillin +tazobactam**	Streptococci, MSSA, G -ve bacilli, N. meningitidis, anaerobes except C. difficile

	Cephalosporins	1st generation	**Cephalexin,** cefazolin	Streptococci except enterococci, MSSA, E. coli, klebsiella, H. influenza, Pepto streptococcus
		2nd generation	Cefuroxime, cefotetan	Like 1st generation + gram - ve bacilli except pseudomonas
		3rd generation	**Ceftriaxone, cefixime,** Cefpodoxime, Cefdinir	Streptococcus except enterococcus, MSSA, G -ve coccobacilli, G -ve bacilli except pseudomonas, Pepto streptococcus
			Ceftazidime	G -ve bacilli, N. meningitidis
		4th generation	**Cefepime**	Streptococcus except enterococcus, MSSA, G -ve bacilli, N. Meningitidis,
	Carbapenems		**Meropenem, Imipenem**	Streptococci, MSSA, G -ve bacilli, N. Meningitides, and anaerobes except C. difficile
			Ertapenem	Streptococci except enterococcus, MSSA, G -ve bacilli except pseudomonas, and anaerobes except C. difficile
	Monobactams		Aztreonam	
Glycopeptides			**Vancomycin**	Gram +ve cocci including MRSA, Pepto streptococcus and C. difficile from anaerobes
Protein Synthesis Inhibitors				
Bactericidal	Aminoglycosides		**Gentamycin, streptomycin, neomycin, amikacin, kanamycin**	**All G-ve bacilli, TB**
Bacteriostatic	Tetracyclines		**Tetracycline (TTC), doxycycline**	Streptococci except enterococci, MSSA, E. coli, klebsiella, H. influenza, pepto streptococcus, Rickettsia, atypical's
	Chloramphenicol (CAF)			Streptococci except enterococci, E. coli, klebsiella, H. influenza, Gram(-ve) coccobacilli, Pepto streptococcus and Bacteroides from anaerobes
	Macrolides		**Azithromycin**	Streptococci except enterococci, MSSA, E. coli, klebsiella, H. influenza, **N. Gonorrhea, C. trachomatis** from atypicals, Rickettsia
			Erythromycin	Streptococci except enterococci, MSSA, atypical's
			Clarithromycin	Streptococci except enterococci, MSSA, E. coli, klebsiella, H. influenza, atypical's except C. trachomatis H. **pylori,**
	Lincosamide		**Clindamycin**	Streptococci except enterococci, Staph epidermidis (CoNS), MSSA, Pepto streptococcus and Bacteroides from anaerobes,
Nucleic acid synthesis Inhibitors				
		1st generation	Nalidixic acid	

Direct enzyme inhibitors	***Fluoroquinolones***	2nd generation	**Ciprofloxacin, Norfloxacin (bladder specific)**, ofloxacin	All G-ve bacilli, N. Meningitidis
		3rd generation	**Levofloxacin**	Streptococci except enterococci, G-ve bacilli except pseudomonas, Pepto streptococcus, atypical's except chlamydia, moxifloxacin is active against bacteroids
		4th generation	Moxifloxacin	
Folate synthesis inhibitors	Sulfonamide Derivatives	Trimethoprim - Sulfamethoxazole (**cotrimoxazole**, TMP - SMX)		MSSA, G-ve bacilli except pseudomonas, P.jirovecii (PCP)
		Pyrimethamine - Sulfadiazine		
		Pyrimethamine — Sulfasalazine		
Miscellaneous				
Nitroimidazole		**Metronidazole**		Anaerobes
Nitrofurantoin (just bladder infection)				Enterococci, E. coli, klebsiella, H. influenza,
Rifampin				Staph epidermidis (CoNS), MRSA and MSSA,

*corelate with the antibiotic sensitivity chart above and with the table below

#Drugs highlighted in bold letters are available in Ethiopia

MRSA = methicillin resistance staph aureus, MSSA = methicillin sensitive staph aureus

CoNS = Coagulase negative staphylococcus (staph epidermidis)

Group of common infectious bacteria

Table; Group of common infectious bacteria with their antibiotic options#

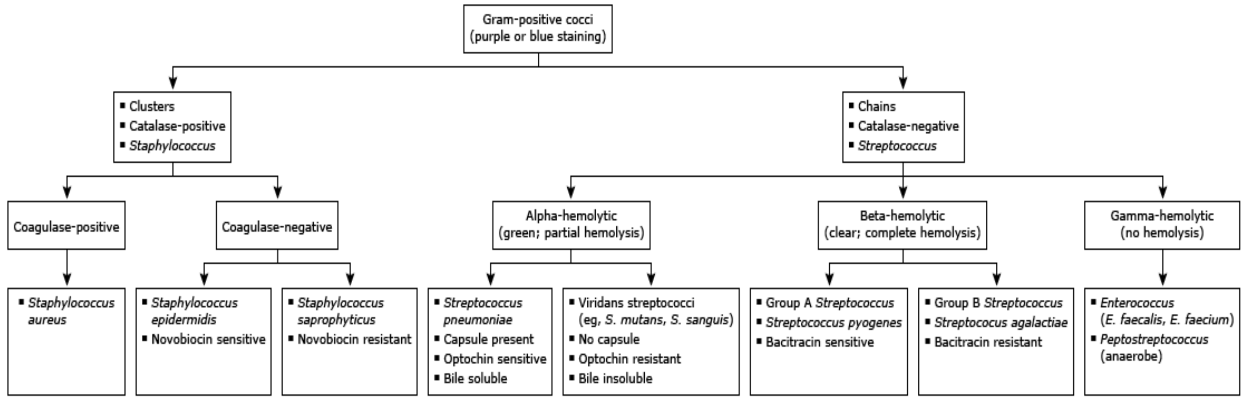
Group		Bacteria	Location	Antibiotics active against the bacteria*
Gram +ve cocci	Streptococci (in chains)	S. pyogenes (GAS), S. agalactiae (GBS), S. pneumoniae, S. viridans	Brain, respiratory tract, oral, heart, skin	All penicillin's except cloxacillin, cephalosporins except ceftazidime, carbapenems, macrolides, Tetracyclines, levofloxacin, clindamycin, chloramphenicol, vancomycin
		Enterococci (Group D strep)	Intraabdominal, urinary tract	All penicillin's except cloxacillin, Meropenem/ imipenem, vancomycin, nitrofurantoin (bladder specific)
	Staphylococci (in clustors)	MSSA	Bone/joint, respiratory tract, oral, heart, skin	Cloxacillin, Augmentin, piperacillin tazobactam, cephalosporins except cefixime and ceftazidime, carbapenems, macrolides, Tetracyclines, clindamycin, cotrimoxazole, vancomycin, rifampin
		MRSA		vancomycin, rifampin
		CoNS (Staph epidermidis, S. saprophyticus)	Skin, prosthetics valves	Cloxacillin, clindamycin, vancomycin, rifampin

Gram -ve bacilli	Non-Beta lactamase producing	E. coli, H. influenza, klebsiella pneumonia	Brain, respiratory tract, urinary tract, intraabdominal	Amoxicillin/ampicillin, Augmentin, piperacillin tazobactam, cephalosporins, carbapenems, clarithromycin, TTC, azithromycin and doxycycline just H. influenza, fluroquinolones, cotrimoxazole, chloramphenicol, nitrofurantoin
	Beta lactamase producing			Augmentin, piperacillin tazobactam, 2nd to 4th generation cephalosporins, carbapenems, fluroquinolones, cotrimoxazole, chloramphenicol, nitrofurantoin
	Extended spectrum Beta lactamase producing	E. coli, klebsiella pneumonia		piperacillin tazobactam, Meropenem/imipenem, fluroquinolones, cotrimoxazole, nitrofurantoin
	SPACE	Serratia, Proteus mirabilis, Actinobacterium sp, Citrobacter sp, Enterobacter sp		Augmentin, piperacillin tazobactam, 2nd to 4th generation cephalosporins, carbapenems, fluroquinolones, cotrimoxazole
	Pseudomonas aeruginosa			piperacillin tazobactam, ceftazidime, cefepime, Meropenem/imipenem, fluroquinolones except levofloxacin,
Gram -ve coccobacilli	N. meningitidis		Brain	Pen. G (IV), Ampicillin (IV), piperacillin tazobactam, 3rd and 4th generation cephalosporins, Meropenem/imipenem, cipro floxacillin, chloramphenicol, rifampin
	N. Gonorrhea		STI/PID	Ceftriaxone, cefixime, azithromycin, chloramphenicol
Anaerobes	Pepto streptococcus		Above the diaphragm (oral, respiratory tract)	metronidazole, Penicillin's except cloxacillin, cephalosporins except ceftazidime and cefixime, Meropenem/imipenem/ ertapenem, tetracyclines, levofloxacin/ moxifloxacin, clindamycin, vancomycin, chloramphenicol,
	Bacteroides		Below the diaphragm (Intraabdominal, PID)	metronidazole, piperacillin tazobactam, Cefoxitin/cefotetan, Meropenem/imipenem/ertapenem, moxifloxacin, clindamycin, chloramphenicol,
	C. difficile		Intraabdominal	metronidazole, vancomycin
Atypical bacteria	Mycoplasma pneumoniae, Chlamydophila species		Respiratory tract	Macrolides, Tetracyclines, levofloxacin/ moxifloxacin
	Legionella pneumophilia			Macrolides, Tetracyclines, ciprofloxacin/levofloxacin/ moxifloxacin
	Chlamydia trachomatis		STI/PID	Azithromycin, Erythromycin, Tetracyclines
Rickettsia	R. prowazekii, R. typhi		Typhus	Doxycycline, TTC, Chloramphenicol, Fluroquinolones,
Borrelia	B. recurrentis, B. hermsii, B. turicatae (New World species), B. duttonii (Old World species)		Relapsing fever	Procaine penicillin, TTC, Erythromycin, cephalosporins

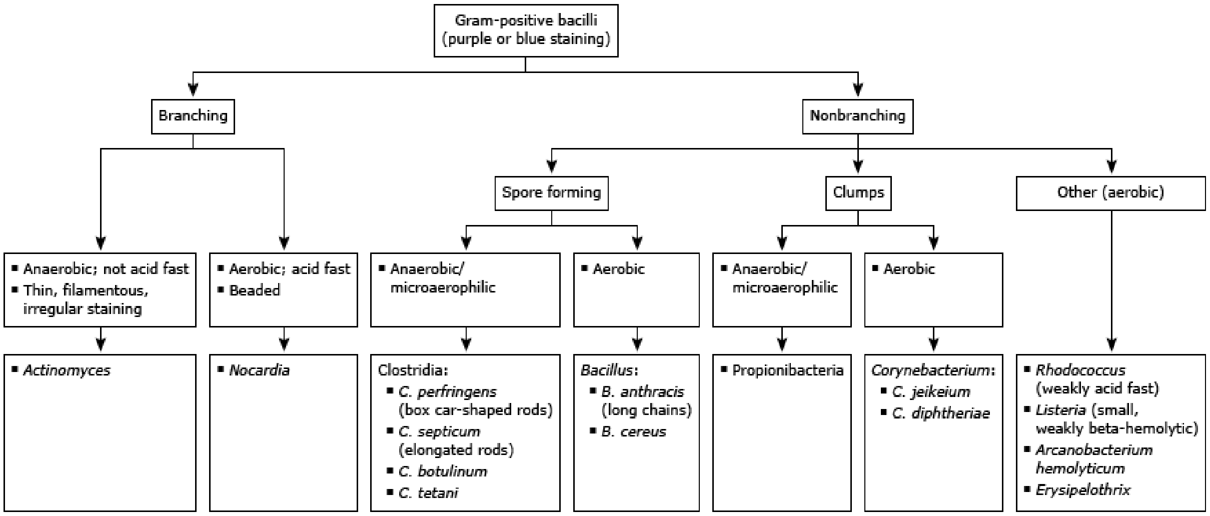
[#] See the classification based on laboratory feature below

*correlate with the above table and sensitivity chart
GAS = Group A streptococcus, GBS = Group B streptococcus

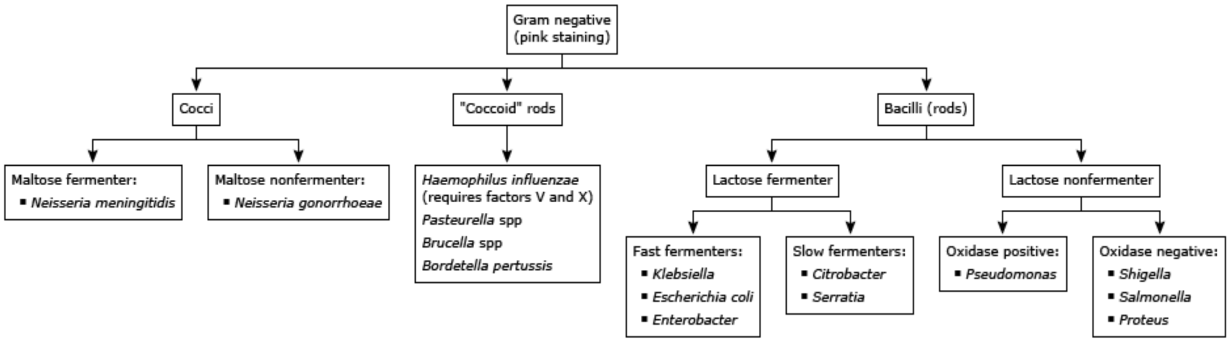
Classification of gram-positive cocci by laboratory features


Gram-positive cocci (purple or blue staining)
Clusters
Catalase-positive
Staphylococcus
Chains
Catalase-negative
Streptococcus
Coagulase-positive
Coagulase-negative
Alpha-hemolytic (green; partial hemolysis)
Beta-hemolytic (clear; complete hemolysis)
Gamma-hemolytic (no hemolysis)
Staphylococcus aureus
Staphylococcus epidermidis
Novobiocin sensitive
Staphylococcus saprophyticus
Novobiocin resistant
Streptococcus pneumoniae
Capsule present
Optochin sensitive
Bile soluble
Viridans streptococci (eg, S. mutans, S. sanguis)
No capsule
Optochin resistant
Bile insoluble
Group A Streptococcus
Streptococcus pyogenes
Bacitracin sensitive
Group B Streptococcus
Streptococcus agalactiae
Bacitracin resistant
Enterococcus (E. faecalis, E. faecium)
Peptostreptococcus (anaerobe)

Classification of gram-positive bacilli by laboratory features


Gram-positive bacilli (purple or blue staining)
Branching
Nonbranching
Spore forming
Clumps
Other (aerobic)
Anaerobic; not acid fast
Thin, filamentous, irregular staining
Aerobic; acid fast
Beaded
Anaerobic/ microaerophilic
Aerobic
Anaerobic/ microaerophilic
Aerobic
Actinomyces
Nocardia
Clostridia:
C. perfringens (box car-shaped rods)
C. septicum (elongated rods)
C. botulinum
C. tetani
Bacillus:
B. anthracis (long chains)
B. cereus
Propionibacteria
Corynebacterium:
C. jeikeium
C. diphtheriae
Rhodococcus (weakly acid fast)
Listeria (small, weakly beta-hemolytic)
Arcanobacterium hemolyticum
Erysipelothrix

Classification of gram-negative organisms by laboratory features


Gram negative (pink staining)
Cocci
"Coccoid" rods
Bacilli (rods)
Maltose fermenter:
Neisseria meningitidis
Maltose nonfermenter:
Neisseria gonorrhoeae
Haemophilus influenzae (requires factors V and X)
Pasteurella spp
Brucella spp
Bordetella pertussis
Lactose fermenter
Lactose nonfermenter
Fast fermenters:
Klebsiella
Escherichia coli
Enterobacter
Slow fermenters:
Citrobacter
Serratia
Oxidase positive:
Pseudomonas
Oxidase negative:
Shigella
Salmonella
Proteus

Chapter 8; Symptoms and signs in Amharic (የበሽታ ምልክቶች አማርኛ ትርጉም)

Dr. Mulualem. G

HEENT related sign and symptoms

- Buldged fontanelle = የእርግብግቢት እብጠት
- Epistaxis = ነስር
- Icteric sclera = የዓይን ቢጫ መሆን
- Increased head circumference = የእራስ ቅል መጨመር

Respiratory system related sign and symptoms

- Chest pain = የደረት ህመም (ደረት ውጋት)
- Cough = ሳል
- Fast breathing (Tachypnea) = ከላይ ከላይ መተንፈስ፣ ቃታ መንሳት
- Hemoptysis = ደም የቀላቀለ አክታ
- Rhinorrhoea = የንፍጥ መብዛት (ማናፈጥ)
- SOB (Dyspnoea) = ትንፋሽ ማጠር
- Sputum = አክታ
- Stridor = ኩርርታ
- Wheeze = ማቃተት፣ የሚአፏጭ ድምጽ

CVS related sign and symptoms

- Edema = ውሃ አዘል ገላ
- Fatigue (easy fatigability) = ድካም
- Intermittent claudication = አልፎ አልፎ በጉዞ ወቅት የሚከሰት የእግር ሕመም
- Leg swelling = የእግር እብጠት
- Orthopnoea = ተንጋሎ ትንፋሽ ማጠር
- Palpitation = የልብ መደንከር
- Tachycardia = ፈጣን የልብ ምት

STI and Gynaecology related sign and symptoms

- Dyspareunia = በግብረ ስጋ ግንኙነት ወቅት ህመም መሰማት
- Vaginal bleeding (abnormal uterine bleeding) = በማህጸን ደም መፍሰስ
- Menstrual irregularitie = የወር አበባ መዛባት
  - Dysmenorrhea = በወር አበባ ወቅት ከፍተኛ የሆነ ህመም ስሜት
  - Menorrhagia/ metrorrhagia = መጠኑ ብዙ የሆነ የወር አበባ መፍሰስ/ ለብዙ ጊዜ መፍሰስ
  - Amenorrhea (10, 20) = አደፍ ቅሪት
- Vaginal discharge = የማህጸን ፈሳሽ ፣ የብልት ፈሳሽ
- Urethral discharge = የብልት ፈሳሽ
- Genital ulcer with/without inguinal swelling = የብልት (ሀፍረተ ስጋ) ቁስል
- chancre = ከርክር

Haematology related sign and symptoms

- Bleeding = ደም መፍሰስ፣ መድማት
- Blurring of vision = የእይታ መደብዘዝ
- Epistaxis's = ነስር
- Light headedness = የራስ መቅለል
- Pallor = መገርጣት
- Tinnitus = ህውታ፣ በጩኸት የሚፈጠር የጆሮ ህመም

MSS related sign and symptoms

- PND = ድንገት በሚመጣ የትንፋሽ ማጠር ምክንያት ከመኝታ ተነስቶ መስኮት ከፍቶ አየር ለማስገባት መሞከር
- SOB (Dyspnoea) = ትንፋሽ ማጠር
- Syncope = ራስን መሳት

GI related sign and symptoms

- Abdominal distension = የሆድ መነፋት
- Abdominal swelling = የሆድ እብጠት
- Abdominal pain = የሆድ ህመም፣ የሆድ ቁርጠት
- Ascites = = ቅምጥ ውሃ ፣ ውሃ የቋጠረ ሆድ
- Constipation = ሆድ ድርቀት
- Diarrhoea = ተቅማጥ
- Dyspepsia = የምግብ አለመፈጨት ችግር
- Dysphagia = የመዋጥ ችግር
- Heart burn (Burning epigastric pain) = ቃር፣ የሚአቃጥል የደረት ህመም
- Hematemesis = ደም የቀላቀል ትውከት፣ ደም ማስተፋት
- Jaundice = የሰውነት ቢጫ መሆን፣ ወይቦ
- Melena = ደም የቀላቀለ ሰገራ
- Nausea = ማቅለሽለሽ
- Odynophagia = ምግብ በመዋጥ ወቅት ህመም መሰማት
- Splenomegaly = የጣፊያ ማበጥ፣ ጓቋ/for VL patient/
- Vomiting = ትውከት፣ ማስመለስ

GUS related sign and symptoms

- ✓ Flank pain = የሽንጥ ህመም ፣ የጎን ህመም
- ✓ Hematuria = ደም መሽናት ፣ ደም የቀላቀል ሽንት
- ✓ Oliguria or anuria = ሽንት ማነስ
- ✓ Polyuria = ብዙ መሽናት
- ✓ Urinary incontinence = ሽንት አለመቋጠር
- ✓ Lower urinary tract symptoms (LUTS):
  - ♥ dribbling = የሽንት መንጠባጠብ፣
  - ♥ **Dysuria** (pain during urination) = **ሽንት ማጥ**
  - ♥ frequency of micturition = በድግግሞሽ (አዘውትሮ) መሽናት
  - ♥ hesitancy = መሽናት እየፈለጉ ግን መሽናት አለመቻል፣
  - ♥ reduced calibre and force of urinary stream = የሽንት ሃይል መቀነስ፣
  - ♥ straining to void = ማማጥ
  - ♥ urgency = አጣዳፊ ሽንት

- Deformity = አካለ ጎደሎነት
- Fracture = ስብራት
- Instability = የሰውነት አለመረጋጋት
- Limping = ማነከስ
- Morning stiffness = የሰውነት ግትርነት (በጠዋት)
- Swelling = እብጠት
- Weakness = ድካም

NS related sign and symptoms

- ☛ Body weakness (weakness of extremities) = የሰውነት መስነፍ
- ☛ Cognitive disturbance = የመገንዘብ ችግር
- ☛ Disturbance in vision, hearing, swallowing = የማየት፣ የመስማት፣ የመዋጥ ችግር
- ☛ Disturbance of speech (dysphasia/aphasia) = የማውራት ችግር፣ ማውራት አለመቻል
- ☛ Headache = ራስ ምታት፣ ራስ ውጋት
- ☛ LOC = ራስን መሳት ፣ እንደሞተ ሰው መሆን
- ☛ Neck stiffness = ማጅራት መገተር
- ☛ Seizure (Abnormal body movement) = እንፍርፍሪት፣ የሚጥል ህመም

Miscellaneous

- → Easy fatigability = ድካም
- → Fever = ትኩሳት
- → Increased appetite = የምግብ ፍላጎት መጨመር
- → Loss of appetite = የምግብ ፍላጎት መጥፋት (መቀነስ)
- → Lymphadenopathy = ፍርንቲት
- → Weight loss = ክብደት መቀነስ

Others

- → Infection = ልክፍት
- → Inflammation = ብግነት
- → Complication = ክፍ ምጪ
- → Risk factor = ለበሽታ አጋላጭ
- → Side effect = የጎንዮሽ ጉዳት

Vaccine Preventable disease (በክትባት ቅድመ መከላከል የሚቻሉ በሽታዎች)

- Measles = ኩፍኝ ፣ አንከሊስ፣ ቋቋት
- Mumps = ጆሮ ደግፍ
- Rubella /German Measles/ = የጀርመን ኩፍኝ
- Varicella (Chiken pox) = ጉድፍ
    - Herepes zoster (shingles) = አልማዝ ባለጭራ
- Diphtheria = ዲፍቴሪያ፣ ተላላፊ የጉሮሮ በሽታ
- Pertussis = ትክትክ
- Tetanus = መንጋጋ ቆልፍ
- Poliomyelitis (Polio) = ልምሻ ፣ ፖሊዮ

N.B vaccines

MMRV = Measles, mumps, rubella, and varicella virus vaccine

DPT = Diphtheria, tetanus toxoids, and acellular pertussis vaccine

Penta valent vaccine contains = DPT, HBV vaccine and Hib (Hemophilus influenza type b) vaccine

8.1 Amharic translation of Selected Dermatologic disorders (የተወሰኑ የቆዳ በሽታዎች አማርኛ ትርጉም)

- Acne Vulgaris = ብጉር
- Bacterial infections of the skin and soft tissue
    - Cellulitis = የቆዳ ብግነት
    - Erysipelas =
    - Carbuncle = ንፍርቅ እባጭ
    - Furuncle
    - Impetigo = ፍንድሽ ቁስል
    - Necrotizing fasciitis
- Fungal Infections of the skin
    - Mucocutaneous Candidiasis
    - Balanoposthitis
    - Candidal Intertrigo
    - Candidal paronychia
    - Vulvovaginitis = የሴት ብልት ብግነት
    - Oral candidiasis (thrush) = የአፍ ፈንገስ ልክፍት
    - T. capitis (ring wom) = ፎረፎር፣ ቆረቆር፣ አጓጉት
    - Pityriasis Versicolor (PV) = ቋቁቻ
- Viral skin disorders
    - Herpes Simplex (HS) = ምች፣ ሽፍታ
    - varicella-zoster (Chicken Pox) = ጉድፍ
    - Herpes zoster (shingles) = አልማዝ ባለጭራ
    - Molluscum Contagiosum
    - Pityriasis rosea
- lice: body and head lice = ቅማል

- scabies = እከክ
    - Itching = የማሳከክ ስሜት
- Atopic Dermatitis (AD) = የቆዳ አስም
- Contact dermatitis = በንክኪ የሚከሰት የቆዳ ብግነት/አለርጂ
- Seborrhoeic dermatitis
- Psoriasis = የሚያሳክክ የቆዳ በሽታ
- Vitiligo
- Albinism = ሻሾት

Chapter 9; anatomical body parts in Amharic (የሰውነት አካል ክፍሎች አማርኛ ትርጉም)

Dr. Mulualem. G

HEENT (ከአንገት በላይ)

- Head = ራስ
    - Hair = ጸጉር
    - SCALP = የራስ ቆዳ
    - Skull = ራስ ቅል፣ ጭንቅላት
- Eye = ዐይን
    - Sclera = የዐይን ጽኑ ልባስ
    - Conjunctiva = ልባሰ ዐይን
    - Pupil = ብሌን
    - Lens = ምስሪት ፣ ሌንስ
    - Eye lid = የዐይን ቆብ
    - Eye lash = ሽፋሽፍት፣ ሽፋል
    - Eye brow = ቅንድብ
- Ear = ጆሮ
    - External, middle and inner ear = ውጫዊ፣ መካከልኛ እና ውስጣዊ የጆሮ ክፍል
    - Eustachian tube = እስታች ትቦ/ቦይ
    - Tympanic membrane/ear drum = የጆሮ ታምቡር
- Nose = አፍንጫ
    - Nostril = የአፍንጫ ቀዳዳ ፣ ዋንፍ
    - Nasal septum = የአፍንጫ ግድግዳ
    - Nasal cavity = ሰርን
- Throat

Lymphoglandular System (ሥርዓተ ፍርንት/ሥርዓተ ሊንፍ/)

- Lymh node = ፍርንትት፣ ፍርንት እጢ/ሊንፍ እጢ
- Lymphatic vessel = ፍርንት ስር
- Lymhatic circulation = ፍርንት ዙረት/ዑደት

Respiratory System (ሥርዓተ ትንፈሳ)

- Larynx = ማንቁርት
- Vocal cord = ሀብለ ድምጽ፣ አውታረ ድምጽ
- Trachea = ትንባ ፣ የአየር ቧንባ
- Bronchi = ቀሳቢት
- Bronchiole = ቀሳቢቴ፣ ደቂቅ ትንባ

Genitourinary System (ስርዓተ ሽንት)

- Kidney = ኩላሊት
- Ureter = ቦየ ፊኛ ፣ ፊኛ ኩልት ቱቦ
- Bladder = ፊኛ
- Urethra = ቦየ ሽንት ፣ ፊኛሽን ቱቦ
- Urethral meatus = ፊኛሽን ቀዳዳ

Reproductive organs (አባለ ወሊድ ፣ የመራቢያ አካላት)

- Uterus = ማህጸን
- Uterine fundus = የማህጸን አናት
- Fallopian tube = ፋሎኘ ፣ የማህጸን ቱቦ
- Ovary = እንቁልጢ --› እንቁላል እጢ
- Cervix = የማህጸን በር ፣ ህጽንተ አንገት
- Vulva = የሴት ብልት ከንፈር/ ቀዳዳ
- Vagina = የሴት ብልት ፣ ከረቤዛ፣ እምስ /ጸያፍ ቃል/፣ ማህጸን/በተለምዶ/
- Clitoris = ቂንጥር
- Labia = ከናፍረ ከረቤዛ፣ ከናፍረ እምስ
    - Labia majora = ዐቢይ ከንፈረ ከረቤዛ
    - Labia minora = ንዑስ ከንፈረ ከረቤዛ
- Scrotum = ማህደረ ቆለጥ፣ የቆለጥ ከረጢት
- Testes = ቆለጥ
- Prostate = ፍስ ውሃ እጢ ፣ ፕሮስቴት እጢ
- Penis = ቁርዝ ፣ ቁላ/ጸያፍ ቃል/፣ እስኪት፣ የወንድ ብልት
- Glans penis

Musculoskeletal System (ሥርዓተ አፅም እና ጡንቻ)

- Skeleton = አፅም
- Bone = አጥንት
    - Vertebrae = አከርካሪ፣ ደንደስ
    - Vertebral bone = የጀርባ አጥንት
    - Scapula = ብራኳ
    - Humerus = አጽመ ወርች፣ የክንድ የላይኛው ቅልጥም

- Lung = ሳንባ
- Pleura = ልባሰ ሳንባ፣ አቃፊ ሳንባ፣
- Pleural cavity = ሳንባ አኑር ወና
- Diaphragm = ብራኔ ፣ ድልሺ /ከኦሮምኛ የተወሰደ/
- Chest = ደረት

Cardiovascular System (ሥርዓተ ልብ እና ሽንዳ)

- Heart = ልብ
  - Left/Right ventricle = ግራ/ቀኝ ሰጭ ልበ ገንዳ ፣ ከረርሰ ልብ
  - Left Right auricle = ግራ/ቀኝ ተቀባይ ልበ ገንዳ
  - Myocardium /Cardiac muscle = የልብ ጡንቻ
  - Pericardium = ልብ ሰፋድል፣ ከባቤ ልብ
  - Pericardial cavity = ልብ አኑር ወና
- Vessel = የደም ስር
  - Artery = ደም ወሳጅ
    - Aorta = ዐቢይ ደም ወሳጅ
    - Arteriole = ንዑስ/ደቂቅ ደም ወሳጅ
    - Capillary = ርቂት፣ ቀጭን የደም ቧንቧ
    - Capillary bed = መረበ ርቂት
  - Vein = ደም መላሽ
    - Vana cava = ዐቢይ ደም መላሽ
    - Venule = ንዑስ ደም መላሽ፣ ደመላሺት

Gastrointestinal system (ስርዓተ እንሽርሽሪት)

- Mouth = አፍ
- Palate = ላንቃ
- Tonsil = አንቃር፣ ቶንሲል
- Uvula = እንጥል
- Tongue = ምላስ
- Pharynx = ጉሮሮ
- Esophagus = ጉሮሮ
- Stomach = ጨጓራ፣ሆድ
- Small intestine = ቀጭን አንጀት
  - Duodenum = ቀዳማይ ቀጭን አንጀት
  - Jejunum = ማእከላዊ ቀጭን አንጀት
  - Ileum = ዳህራይ ቀጭን አንጀት
- Large intestine = ወፍራም አንጀት
  - Cecum = ጓዳ አንጀት
  - Colon = ትልቅ አንጀት
  - Sigmoid colon = ሲግማሰል ደንዳኔ
  - Rectum = ሬብ፣ ሽለላ አንጀት፣ ትልቅ አንጀት
- Peritoneum = መርመሬ
- Anus = ፊንጢጣ፣ ቱሊ

  - Ulna = ክርን አጽም
  - Radius = የእጅ አጭሩ አጥንት
  - Pelvic bone = ዳሌ አጥንት
  - Pelvic cavity = ዳሌ ጎታ
  - Femur = አጽመ ጭን፣ የጭን አጥንት
  - Patella = የጉልበት ሎሚ
  - Tibia = አጽመ እግር፣ ውስጠ አጽመ ባት
  - Fibula = ምርጊዝ ፣ ውጭ አጽመ ባት
- Muscle = ጡንቻ
- Neck = አንገት
- Arm = ክንድ
- Fore arm = ክንድ
- Hand = እጅ
- Finger = ጣት
- Flank/ loin = ሽንጥ፣ ወገብ
- Buttock = ቂጥ፣ ዳሌ፣ መቀመጫ
- Thigh = ጭን፣ ታፋ
- Leg = እግር
- Calf = ባት
- Foot = ጫማ
- Toe = የእግር ጣት
- Joint = መገጣጠሚያ
  - Shoulder joint = የትከሻ መገጣጠሚያ
  - Elbow joint = የክርን መገጣጠሚያ
  - Wrist joint = የእጅ አንጓ መገጣጠሚያ
  - Hip joint = የሽንጥ/የዳሌ መገጣጠሚያ
  - Knee joint = የጉልበት መገጣጠሚያ
  - Ankle joint = የቁርጭምጭሚት መገጣጠሚያ

Nervous System (ሥርዓተ ነርቭ)

- Skull = ራስ ቅል፣ ጭንቅላት
  - Frontal bone = ግምባር
  - Temporal bone = ጆሮ ግንድ
  - Parietal bone = ጣባ
  - Occipital bone = ራስ ግርጌ
- Brain = አንጎል
  - Cerebrum = አንጎለ አእምረት
  - Cerebral hemisphere = ገሚስ አንጎለ አእምረት
  - Cerebellum
  - Medulla oblongata = ሰረሰርጌ አንጎል
- Spinal cord = ህብለ ሰረሰር
- Nerve = ነርቭ
- Neuron = ሕዋስ ነርቭ

- Hepatic duct = ቦየ ጉበት
- Hepatic portal vein = ጉበታዊ አቀባይ ደም መላሽ
- Spleen = ጣፊያ
- Pancreas = ቆሽት ፣ መረጭ፣ ጣፊያ/በተለምዶ/፣ ፓንክሪስ
- Liver = ጉበት
- Gall bladder = የሀሞት ከረጢት

Chapter 10; Common Laboratory Investigations with practical points and procedures

Dr. Mulualem. G

Here we will discuss selected hematologic, chemistry, Hormone and Chemokine analysis, serologic, and microbiological tests[22]

Basic hematologic tests include;

- CBC (Complete blood count)
    - M. HCT (Manual hematocrit)[23]
    - Hgb (Rapid hemoglobin strip test)[24]
- ESR (Erythrocyte sedimentation rate)
- BF (Blood film)
- PM (Peripheral morphology, peripheral blood smear)
- Basic Immunohematology Tests
    - BG & RH (Blood Group and RH determination), crossmatch

Basic Clinical chemistry tests

- Serum Glucose level → **RBS, FBS, OGTT, HbA_{1C} (Glycated hemoglobin) test**
- LFT (Liver function tests) → Classified in 3 groups:

---

[22] Sample for hematology and serology collected by CBC bottle, while sample for chemistry, hormone and chemokine analysis collected by organ bottle.

[23] Sample for M.HCT collected with capillary tube and at least 2/3rd of the tube should be filled for better out come

[24] If M.HCT is available no need of rapid Hgb test. It is used in peripheral setups where CBC machine or M.HCT are not available. Hgb = 1/3rd of hematocrit

  - Synthetic function: **albumin, PT & aPTT**
  - Metabolic activity: **bilirubin**
  - Cholestasis or biliary obstruction: **ALP, Gamma Glutamyl Transferase (GGT)**
- Liver enzymes → indicate hepatocyte injury: **AST (SGOT), ALT (SGPT)**
- RFT (Renal function test) → **BUN and creatinine**
- Serum electrolyte tests → **NA^+, K^+, Cl^- Ca^{++}, Mg^{++}**
- Body fluid analysis → **CSF analysis, pleural fluid analysis, ascitic fluid analysis, wound discharge analysis**[25]
- Lipid profile tests → **Triglyceride, CL (cholesterol), LDL, HDL**
- Coagulation profile → **PT, aPTT, & INR**
- **Serum Uric acid**
- **Troponin and Creatine kinase**
- **B-type natriuretic peptide (BNP)**
- **Lactate dehydrogenase (LDH)**

3.2 Basic Hormonal analysis tests

- ✓ TFT (TSH, T4, T3)
- ✓ Calcitonin
- ✓ Erythropoietin
- ✓ FSH (Follicle stimulating hormone) and LH (luteinizing hormone)
- ✓ Serum HCG
- ✓ Progesterone
- ✓ Testosterone

3.3 Basic chemokine analysis tests

- ✓ PSA (prostate specific antigen)
- ✓ Alpha fetoprotein (AFP)
- ✓ CA 125, CA 19-9
- ✓ CEA (Carcinoembryonic antigen)

4. Basic clinical Serology tests include;

- Urine HCG
- Widal test
- Weil-Felix reaction
- PICT
- Rapid malarial test
- H. Pylori stool Ag and serum Ab test
- HBsAg (Hepatitis B virus surface antigen) test
- HCV ab (Hepatitis C virus antibody) test
- RK- 39
- VDRL (Venereal Disease Research Laboratory) and RPR
- RF
- ASO titer

5. Basic Microbiological tests

- Gram stain

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[25] Samples from body fluids should be collected by sterile tubes (look at images in culture section below).

- AFB (Aid fast bacilli)
- Culture[26]

Practical points about sample collection [at bedside][27]

- Hematology
  - Sample for hematology is taken by **CBC bottle**[28]. For ESR, collect adequate volume of blood which is more than the volume of sample required for CBC. you can request ''CBC with ESR'' in one request from one sample
  - After taking sample **mix gently and immediately** to prevent coagulation
  - ''CBC, BG & RH, Cross match'' can be done from one sample of a patient. But, in most setups CBC is done in hematology section of the laboratory while BG &RH done at blood bank (or mini blood bank). So, the technician working in hematology may discard the sample after doing CBC. To avoid this, request two papers like below
    - Request #1 → ''CBC, please send sample to BG and RH''
    - Request #2 → ''BG & RH, Cross match''
- Chemistry
  - Sample for chemistry is taken by **Organ bottle**
  - Coagulation profile have its own bottle
  - **Don't shake or mix the sample !!!**
  - During sample collection for **serum electrolyte**, after drawing venous blood, **remove the needle from the syringe** then transfer sample from syringe into organ bottle. This is to prevent hemolysis which significantly affect electrolyte determination
- Sample for **serology also collected by CBC bottle**
- For culture → look at specific topic below
- ***Finally, unless you level the sample (at least by MRN and Pt' name), all the above note will be meaningless.***

EDTA
2.0ml
K2EDTA
vacutube
vacutube
vacutube

---

[26] Blood culture is collected with specific blood culture bottles following possible sterile techniques. Culture from other samples (e.g, CSF, Ascitic fluid, stool and urine) can by collected with sterile tubes (sterile urine cup for urine sample) → look at images in culture section below

[27] **This topic is included in this text, considering most setups of Ethiopia where job description is not applied, and majority of work load given for medical interns. The note is also very essential for medical laboratory and other health science students.**

[28] we use the term CBC bottle to say EDTA tube)

Picture; **CBC bottles** (EDTA blood tubes for Hematology test); These bottles are generally used **for haematology tests** where whole blood is required for analysis. They have **EDTA** (Ethylene diamine tetra acetic Acid) as an additive which Removes calcium, to **prevent blood clotting**.

Picture; **Organ bottles** (SST Tube with Gel and Clot Activator); SST Tube are used to collect blood **for clinical biochemistry and immunology**. They can improve serum surface and prevent substance exchange between blood cell and serum. Guaranteeing biochemical character and chemical components of serum unchanged evidently for a long time, which do not need to us special tool to transport serum. SST = Serum separator tube

PT TUBE SODIUM CITRATE 3.2%
xinle
Sodium Citrate 3.2%(1:9)
2.7ml

Picture; **bottles for coagulation profile/PT, aPTT and INR/** sample collection (Blood PT Tube, Blood Collection PPT Tube, Sodium Citrate Tube); these bottles have Sodium Citrate as an additive which Binds and Forms calcium salts to remove calcium and finally prevent blood from clotting

10.1 Basic Hematology tests

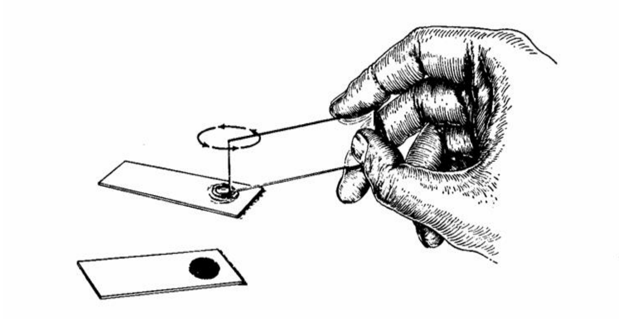
10.1.1 BF (Blood film)

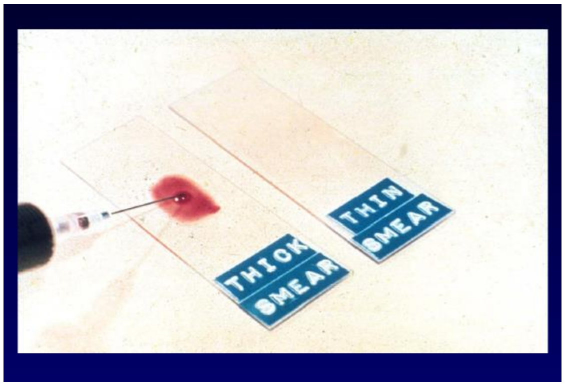
- Blood film is done after preparing blood smear and staining with Giemsa stain

- The term Giemsa stain originated from a name of German chemist and bacteriologist Gustav Giemsa.
- Reagents Required → Methanol, Giemsa powder, Glycerin, Water (Buffer)
- Time of sample collection
  - When the patients feels febrile
  - Before anti-malaria drugs are given to the patients

Preparation of thick films

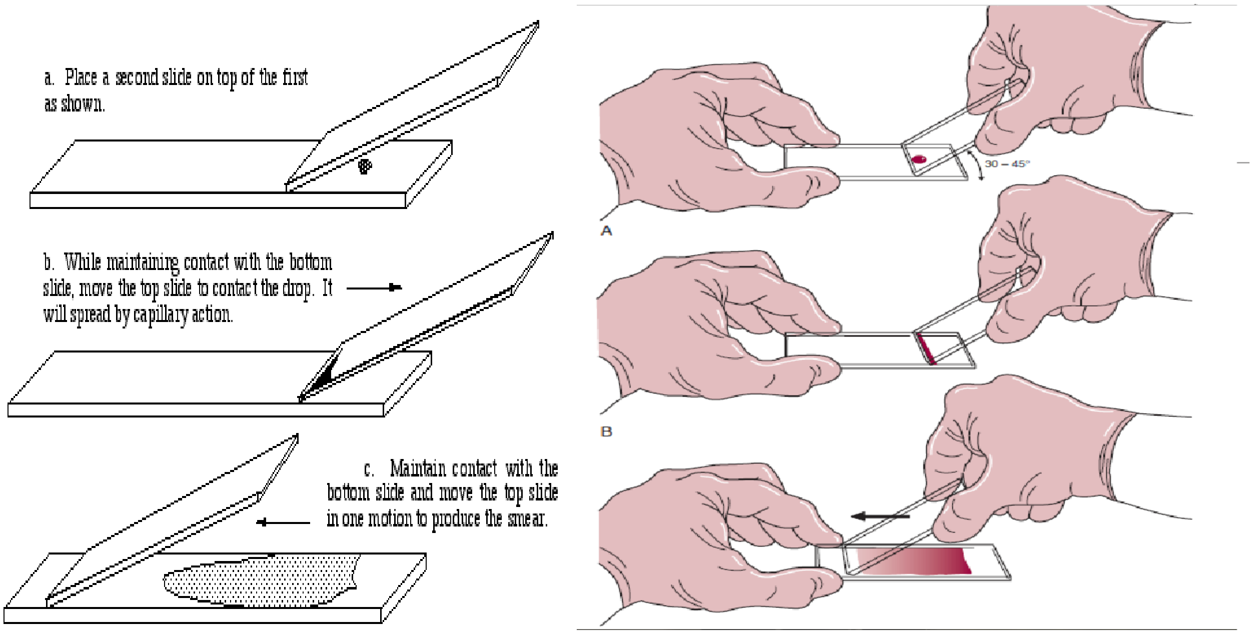
- slides must be clean, free from dirt, grease and fingerprints
- Mix the blood
- Using an applicator stick, apply 4 drops of blood on to a microscope slide
- Spread the blood without excessive stirring to form a smear approximately a cm^2, through which newspaper print can be red. This should be approximately 5 red blood cells thick.
- Allow to air dry horizontally (without using heat).
- Label slides.



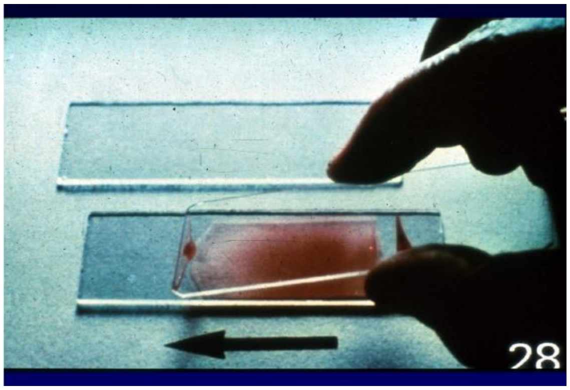


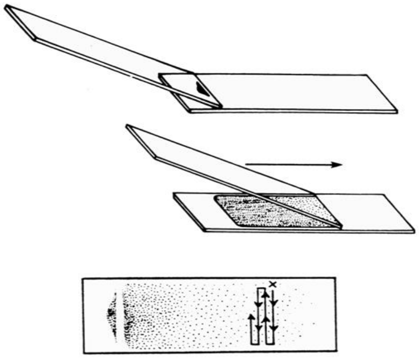
preparation of thin blood smear

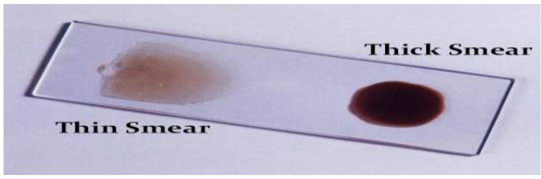
- The microscope slides must be clean as for thick films otherwise the blood will not adhere and the smear will be irregular.
- Apply 1 drop of blood to the end of the slide, pace another slide at an angle of 45° and bring it towards the drop of blood.
- As soon as it touches it, the blood will disperse along the width of the slide.
- Before it reaches the edges, pull the drop along the length of the slide.
- the correct amount of blood in the drop the film will form a good tail before the end of the slide. The film here should be 1 RBC thick. Make 2 slides for each test.
- Air dry, Label slides


a. Place a second slide on top of the first as shown.
b. While maintaining contact with the bottom slide, move the top slide to contact the drop. It will spread by capillary action.
c. Maintain contact with the bottom slide and move the top slide in one motion to produce the smear.
30 – 45°
A
B

Diagrams; steps of thin Blood smear preparation






Thick Smear
Thin Smear

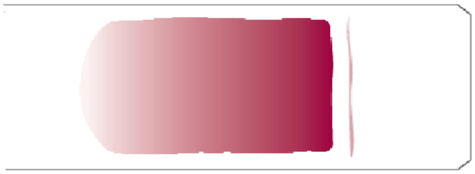
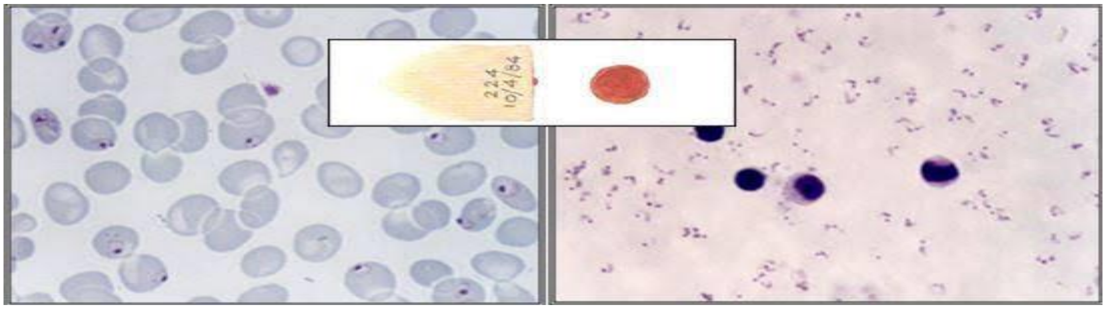


Figure 15-3 Well-made peripheral blood film.

- **Thick film** considered **"gold standard" for detection of parasites** due to being able to use larger volume (10µl of blood)
- **Thin film** considered **"gold standard" in species identification**
- Smear examinations should be under oil immersion
- Negatives should not be reported until 200 oil immersion fields have been examined
- Additional specimens should be examined at 12-hour intervals for a subsequent 36 hours.
- **Taking sample during febrile episodes of the patient increase positivity of the result**
- Mixed infections or low parasitemia usually difficult to diagnose.

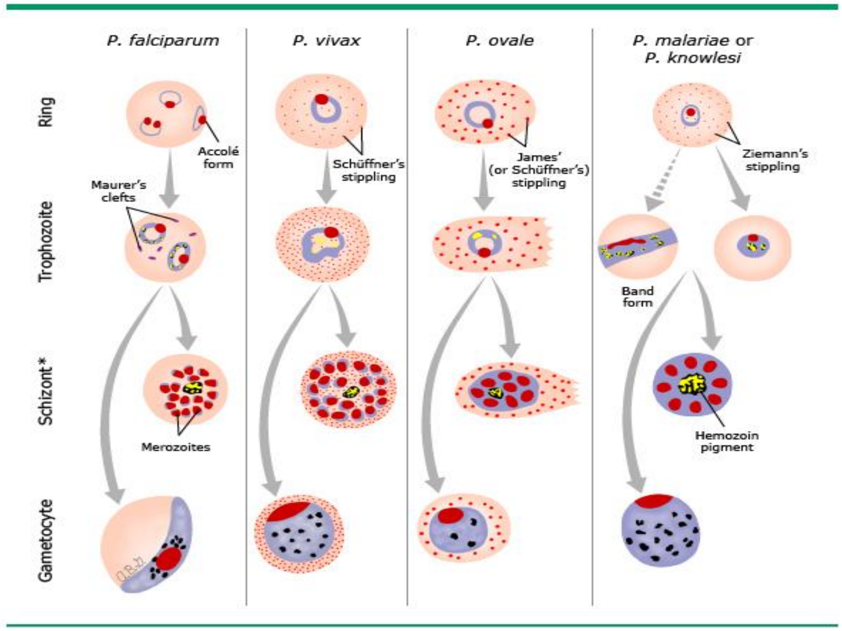


Giemsa Preparation and staining procedure

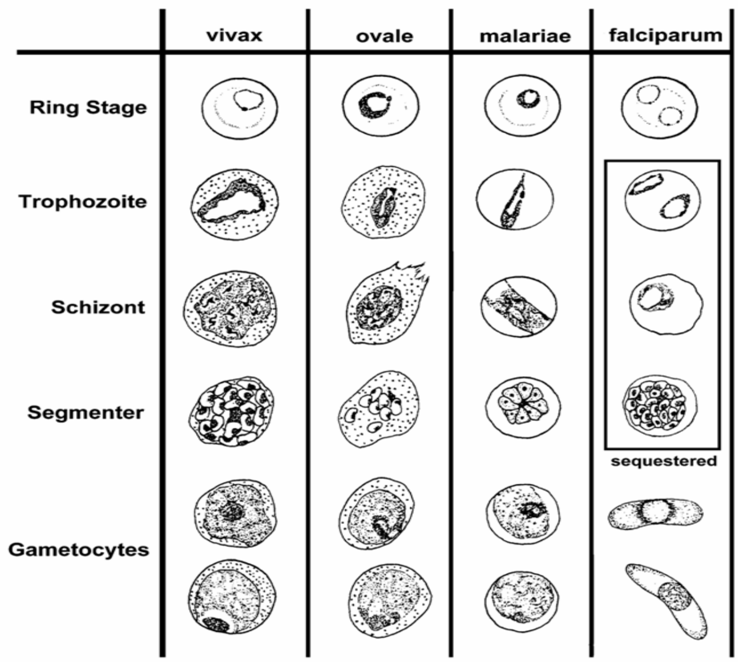
- Reagent
    - Giemsa powder
    - Buffered water, pH 7.1-7.2 or
    - Buffered saline water, pH 7.1-7.2
- **10% solution for 10 minute staining**
    - Measure 45 ml of buffered water in 50 ml cylinder
    - Add 5 ml of Giemsa stain to 50 ml mark
    - Mix gently
- **Gently immerse the slide into a methanol solution for proper fixation of the thin smear. But, Do not fix thick films.**
- Allow to air dry.
- Place the slides in a staining rod/rack
- Cover the air-dried smear with a 1:10 diluted Giemsa using buffered distilled water at pH 7.2 (recommended for malaria parasites in order to stain schuffner's granules) as a diluent
    - 1:10 Giemsa =1 part of stock Giemsa + 9 parts buffered water
- stain the slides as follows:
    - 30 min if using 3% stain solution
    - 10 min if using 10% stain solution
- Wash the stain from the slide gently using clean water (not necessarily distilled water or buffered water)
- Wipe the back of each slide clean and place it in draining rack for the preparation to air dry.
- Now observe the smear under a microscope.
    - Focus on the film with the X10 objective.
    - Examining the film first with 40x objective to select a well stained area
    - Apply a drop of immersion oil on the slide and switch to the oil-immersion objective (100).
    - Examine at least 100 fields(100Xobjective)
    - **P.malariae* exam approximately 200 fields

☛ **Note: Avoid drying of smear by an incubator or by heat, because it may fix the blood smear onto the slide and results in lysis of RBCs.**

Red blood cell morphology in various forms of *Plasmodium* infections

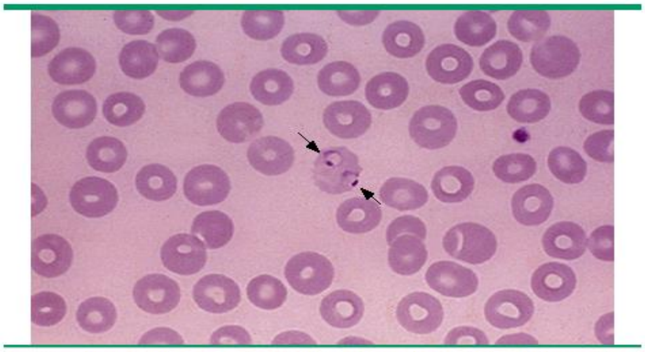

P. falciparum
P. vivax
P. ovale
P. malariae or P. knowlesi
Ring
Trophozoite
Schizont*
Gametocyte
Accolé form
Maurer's clefts
Schüffner's stippling
James' (or Schüffner's) stippling
Ziemann's stippling
Band form
Merozoites
Hemozoin pigment

* Identification of a schizont with >12 merozoites in the peripheral circulation is an important diagnostic clue for *P. vivax*. In general, schizonts of *P. falciparum* are very rarely seen in blood films; they are generally absent from the peripheral circulation except in cases of severe infection with overwhelming parasitemia.

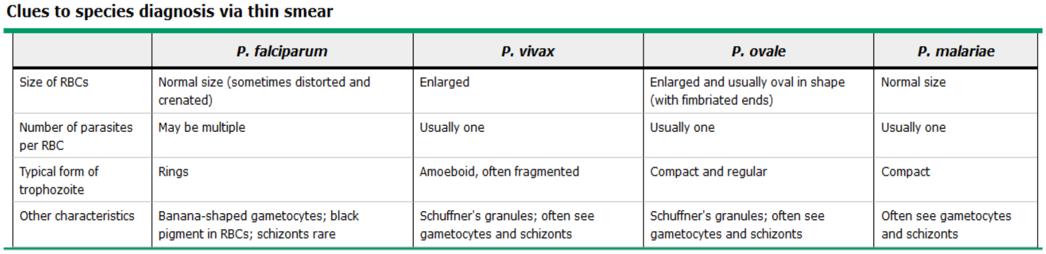

vivax
ovale
malariae
falciparum
Ring Stage
Trophozoite
Schizont
Segmenter
Gametocytes
sequestered

Picture; Stages in humans

Malaria: Red cell containing intraerythrocytic ring forms (trophozoites)



Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows).



Clues to species diagnosis via thin smear

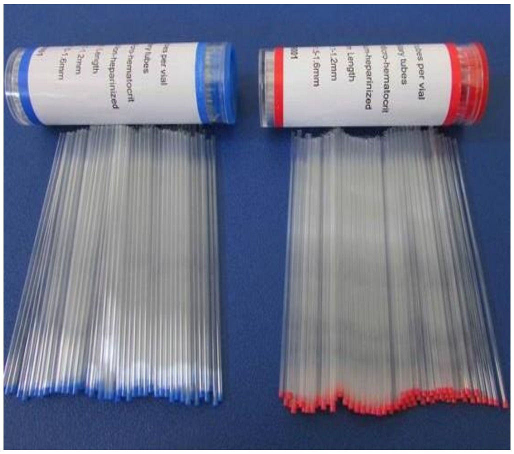
	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*
Size of RBCs	Normal size (sometimes distorted and crenated)	Enlarged	Enlarged and usually oval in shape (with fimbriated ends)	Normal size
Number of parasites per RBC	May be multiple	Usually one	Usually one	Usually one
Typical form of trophozoite	Rings	Amoeboid, often fragmented	Compact and regular	Compact
Other characteristics	Banana-shaped gametocytes; black pigment in RBCs; schizonts rare	Schuffner's granules; often see gametocytes and schizonts	Schuffner's granules; often see gametocytes and schizonts	Often see gametocytes and schizonts

- **A negative test DOES NOT rule out malaria.**

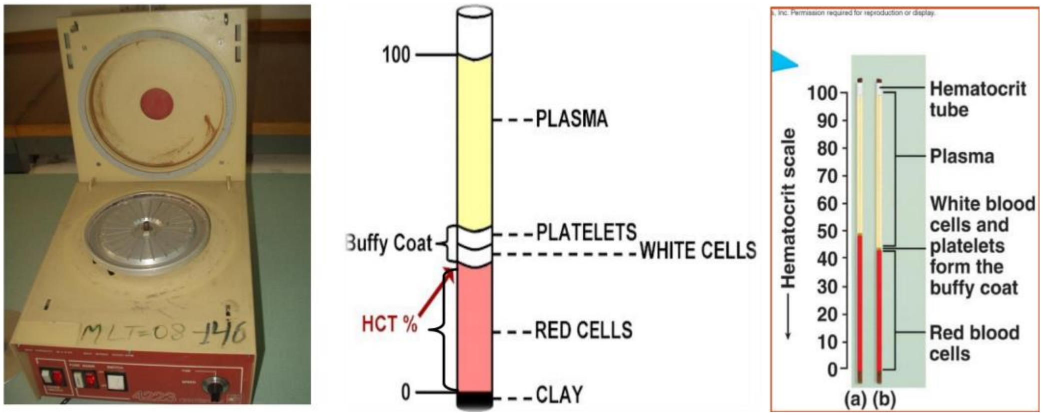
Blood smear and geimsa stain - Click on the link below and watch the video https://youtu.be/uVaYuq6Jzk4

10.1.2 Manual hematocrit (M.HCT)

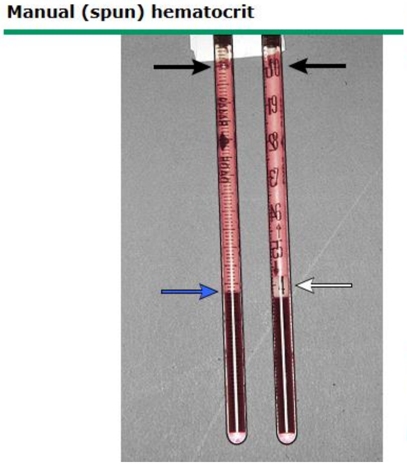
- Sample for M.HCT, collected with capillary tube and at least 2/3rd of the tube should be filled for better out come
- Sample should be taken through the red/blue mark of Capillary tube which have coated anticoagulant

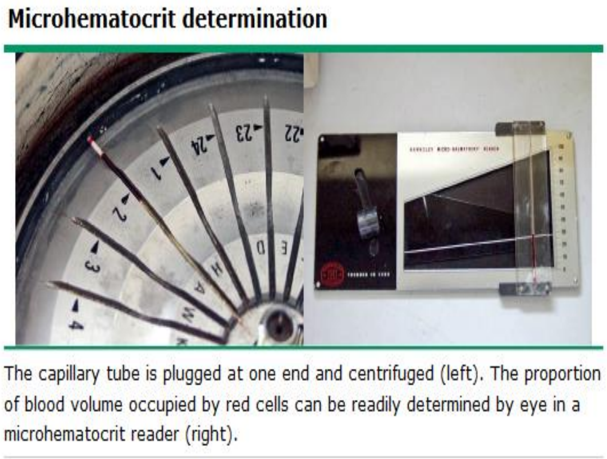


Picture; capillary tubes


MLT=08-146
100
PLASMA
Buffy Coat
PLATELETS
WHITE CELLS
HCT %
RED CELLS
0
CLAY
Hematocrit scale
100
90
80
70
60
50
40
30
20
10
0
Hematocrit tube
Plasma
White blood cells and platelets form the buffy coat
Red blood cells
(a) (b)

Pictures; Hematocrit determination after centrifugation. Left) centrifuge machine. Right) In this particular picture, HCT measured with hematocrit scale is ≅ 50% (a) and ≅ 45% (b)


Manual (spun) hematocrit


Microhematocrit determination

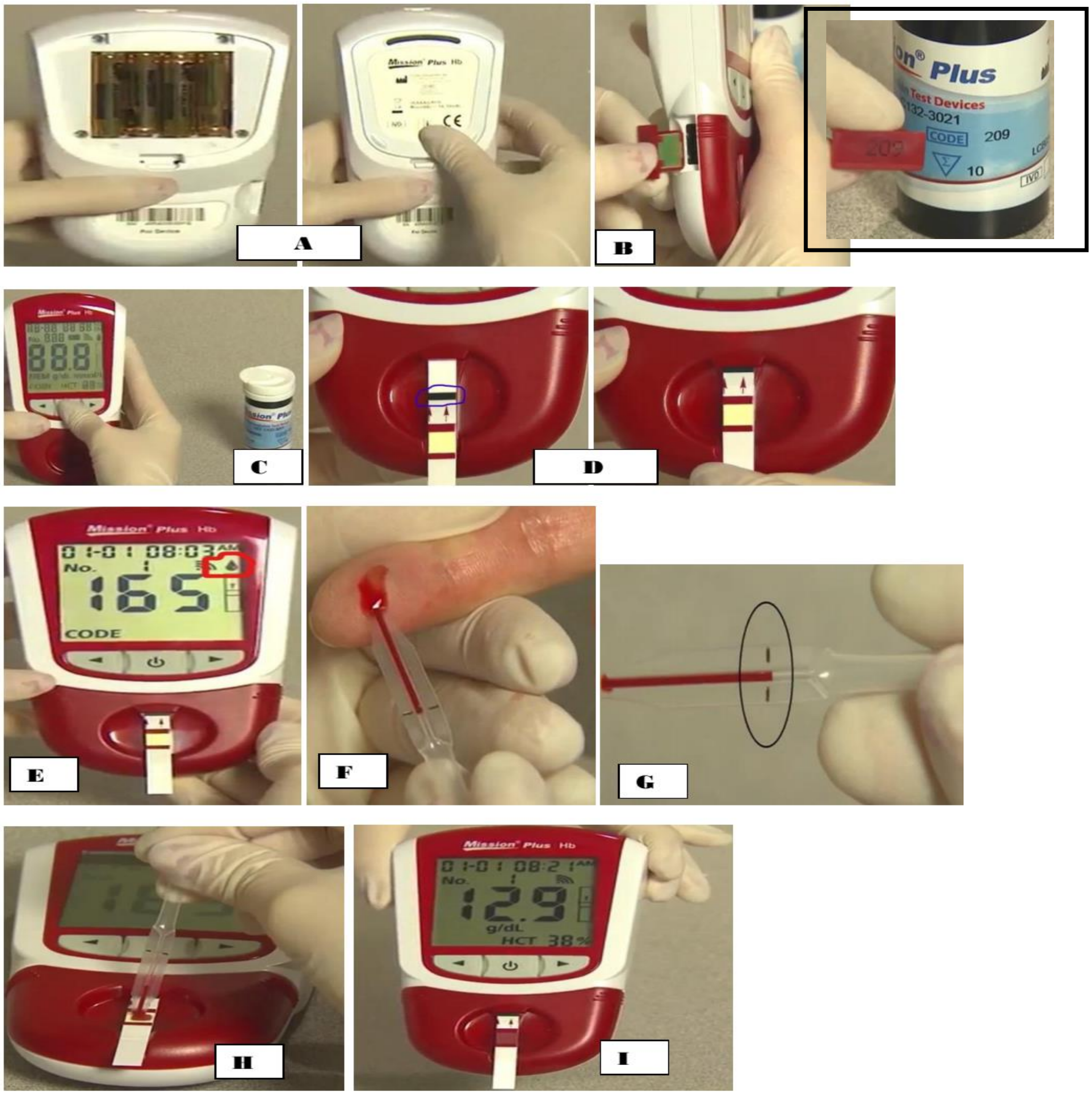
The capillary tube is plugged at one end and centrifuged (left). The proportion of blood volume occupied by red cells can be readily determined by eye in a microhematocrit reader (right).

This photo(left) shows two anticoagulated blood-filled Wintrobe hematocrit tubes following high speed centrifugation. The tube on the left is from a normal subject, with a hematocrit of 38 percent (blue arrow). The tube on the right is from a 19-year-old female with essential thrombocytosis, a normal white blood cell count, and a platelet count of 5,000,000/microL. The extreme degree of thrombocytosis can be appreciated by the presence of a marked increase in the size of the "buffy coat" (white arrow). When the Wintrobe tube is filled to near capacity (upper arrows), and the white blood cell count is not markedly elevated, the platelet count can be estimated by the thickness of this layer, with each mm being equivalent to one million platelets/microL. In normal subjects, the buffy coat, which is comprised of white blood cells and platelets, is only minimally visible.

10.1.3 Hemoglobin (Hgb) Determination

Mission® Plus
Hb Hemoglobin Testing System
Accurate
Portable
Convenient
Quick Reference Guide
①
②
③
④
⑤
- - -
12.4 g/dL

Picture; Hemoglobin test meters (equipment's) or hemoglobin meters


A
B
On® Plus
Test Devices
132-3021
CODE 209
10
IVD
C
D
Mission® Plus Hb
01-01 08:03 AM
No.
165
CODE
E
F
G
H
Mission® Plus Hb
01-01 08:21 AM
No.
12.9
g/dL
HCT 38%
I

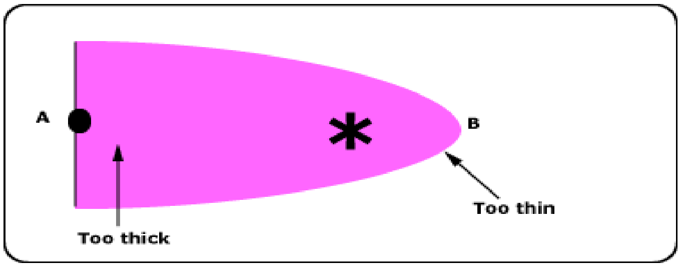
Picture; steps of Rapid hemoglobin determination using ''mission plus hemoglobin testing system''

A) **Insert 4 batteries** into the battery compartment, **close the battery cover** and make sure the snap is shut down
B) **Insert the correct "code chip"** into the "code chip slat" on the meter. Compare the code number on the code chip with the code number printed on test strips canister or the code device. Results will be inaccurate if the two numbers are not identical.
C) **Turn on the meter.** "Setting up the Meter" before testing is necessary which includes; correcting test number setup incase to test up to 999 tests with one memory of the meter, setting 12h or 24h mode, time setup (the date, month and year), setting units (g/dl, g/L or mmol/L) → download and watch the video from the link attached below
D) **Insert the test strip** into the test channel in the same direction as the arrows indicate on the strip. Make sure that, the test strip is inserted all the way to the end of the channel (insert the strip up to the encircled black line in the picture)
E) The **"blood drop symbol"** will flash when the meter is ready for the specimen to be applied
F) **Collect capillary blood of 10 µl** using a capillary transfer tube or pipette. The capillary transfer tube will fill automatically
G) **Make sure the blood covers the end of capillary transfer tube** and never squeeze the tube
H) **Apply the blood sample to the central region of specimen application area** of the test strip
I) **Results** will be displayed in about 15 seconds with Hgb and HCT values as shown in the figure (Hgb = 12.9g/dl, HCT = 38%)

Mission Plus Hb Hemoglobin testing system - Click on the link below and watch the video
https://youtu.be/WO7HApAUSME

10.1.4 PM (Peripheral morphology)

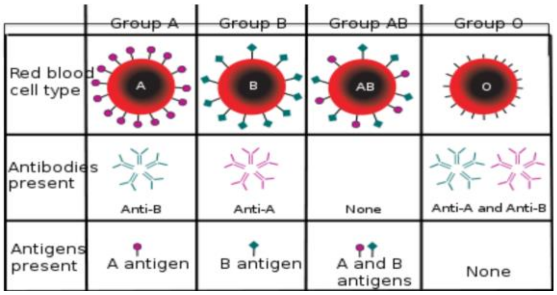
- Smear preparation for PM is the same as malarial thin smear preparation (look at the section of BF above).
- Review of the peripheral smear starts with **choosing the best prepared and stained slide** for examination. Scanning the entire slide under low power enables selection of an optimal area



Diagram; This schematic depicts a well-made peripheral blood smear. A drop of blood has been placed on the left-hand side of a clean glass slide at point A, and has been pulled towards the right-hand side using another glass slide, stopping at point B. The area near point A is too thick and too darkly stained for interpretation, whereas the area at the very end of the smear, near point B (the "feather edge") is too thin, distorting the morphology of all cells in that area. The optimal area for viewing is just behind point B (shown by the asterisk), in an area where the red blood cells are just touching and demonstrate central pallor.

- There are various staining methods for PM, but most laboratories employ Wright-Giemsa staining (look at BF section above)
- For certain cases (e.g. Hematologic malignancy), pathologist evaluation of a well-prepared smear is mandatory. Others (e.g anemia) can be evaluated by laboratory technologist or experienced physicians.
- Look at different morphologies of peripheral Blood smear from anemia section under miscellaneous part of Nitsibin short cases. (click here →Anaemia (የደም ማነስ))

10.1.5 Blood group and RH (BG & RH) determination, cross match



	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies present	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens present	A antigen	B antigen	A and B antigens	None

Figure; Landsteiner's Rule; Reciprocal antibodies are present in the sera of normal people whose RBCs lack the corresponding antigen(s)

ABO phenotyping has two components:

- Forward grouping → Direct (cell grouping)
  - Testing of the red blood cells for the presence of ABO Antigens (or forward grouping).
- Reverse grouping → Indirect (serum grouping)
  - Testing of serum or plasma for the expected ABO Antibodies (or reverse grouping).

slide grouping

- Specimen
  - Patient's serum
  - Patient's cells
- Reagents and equipments:
  - Anti- A and anti-B serum
  - Group O serum (anti-AB)
  - Antigen A and antigen B (20% known RBC suspension)
  - Group AB serum (Control)
  - Tile or slide

- Interpretation
    - Positive agglutination → antibodies specific for A/B antigen are present.
    - Negative agglutination → no antibodies are present for antigens

Rh- typing

- The importance of Rh typing
    - Administration of Rh +ve blood to Rh -ve may sensitize the person to form anti-D antibody.
    - Donation of Rh +ve blood to recipient having anti D could be fatal.
- RBCs (D-Ag) + Anti -D (antisera) → ± agglutination (ag- ab rxn)
- This can be performed on **slide test**, saline tube test, modified tube test
- Interpretation
    - If there is **agglutination** of RBCs -------- positive for D- antigen **(Rh positive)**
    - If there is **no agglutination** of RBCs -------- the D- antigen is not ex pressed. This can be **Rh negative or Du variant**.

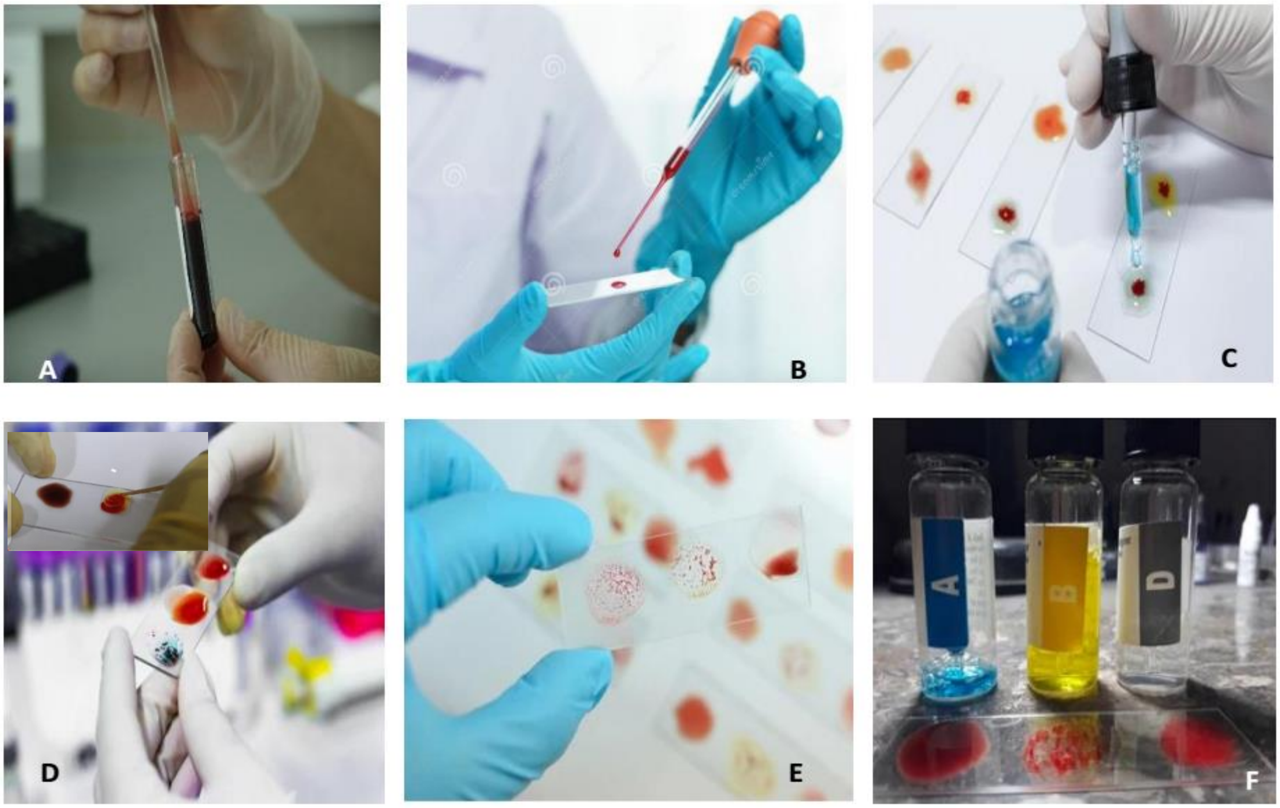
Rh: Weak (Du) variant

- It is weak form of D antigen.
- Negative by direct (cell) typing, must be further tested for the presence of Du variants by indirect antiglobulin test.
    - Blood donor **- as Rh positive**
    - Blood recipient **— as Rh negative**

Blood grouping on glass slide and Result interpretation

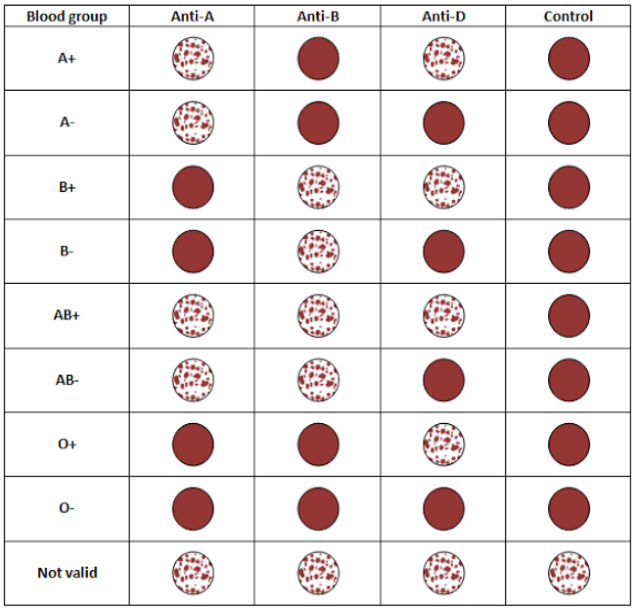
Anti-A
MONOCLONAL ANTIBODIES
Store at 2-8°C
DO NOT FREEZE
Anti-B
MONOCLONAL ANTIBODIES
Store at 2-8°C
DO NOT FREEZE
Anti-D
Store at 2-8°C
DO NOT FREEZE

Picture; Reagents for blood grouping (Anti - A, Anti - B and Anti - D)



Pictures; steps of blood grouping

A) Take blood sample from the bottle
B) Drop blood to the slide glass (4 blood sample drops are required for Anti - A, Anti - B, Anti - D and control)
C) Add the reagents to each blood sample drop on slide
D) Mix the antibody reagents with blood using plastic sticks (as shown in the left upper corner image), then rotate the slide gently to mix blood sample and reagent; caution not to mix one sample drop with the other
E) Check agglutination and report the result
F) Final result of blood group ‘’B^{-} (B negative)’’; which is reactive for Anti - B only (no reaction on Anti - A and Anti - D) → look at the chart below



Blood group	Anti-A	Anti-B	Anti-D	Control
A+	◍	●	◍	●
A-	◍	●	●	●
B+	●	◍	◍	●
B-	●	◍	●	●
AB+	◍	◍	◍	●
AB-	◍	◍	●	●
O+	●	●	◍	●
O-	●	●	●	●
Not valid	◍	◍	◍	◍

Picture; Blood group interpretation chart based on agglutination reaction

Click on the links below and watch the video

Blood grouping experiment - Amrita University

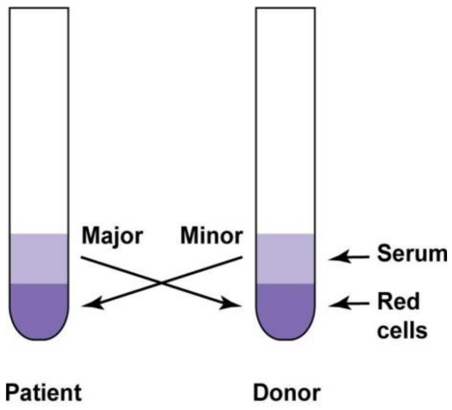
https://youtu.be/-jKzLLHjRfs

Blood Group test or Blood typing

https://youtu.be/Vp19SgV_BMA

Cross matching

- It is the last phase of pre transfusion testing
- It will detect ABO or Rh incompatibility
- There are two kinds of cross match.
  1. Major cross match
  2. Minor cross match



Picture; Major vs Minor Crossmatch

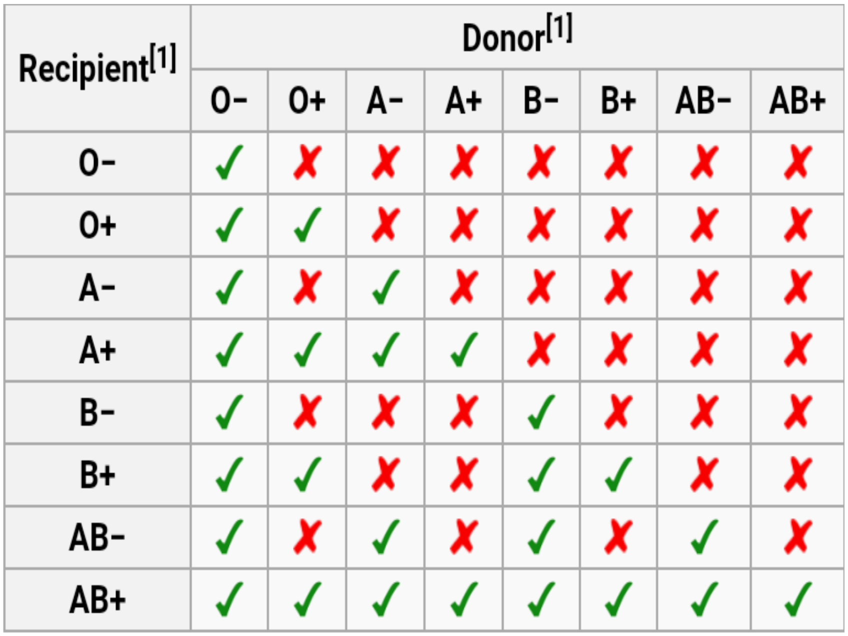
Major cross match

- Detects **antibodies** in the **recipient's serum** that may damage the cells of proposed serum.
- Recipient serum + Donor RBC → agglutination or hemolysis.
- Called major b/c the Abs in the recipient's serum are most likely to destroy the donor's RBC
- **Result:**
  - ✓ Agglutination / hemolysis ----- incompatible
  - ✓ No agglutination/ hemolysis ------compatible

Minor cross match

- Detect **antibodies** in **donor's serum** capable of affecting the RBC of the recipient.
- It has minor importance.
- Involves testing/mixing the **donor's serum** with **recipient's red cells**.
  - ✓ **Donor serum** + **recipient RBC** → agglutination/ hemolysis.
- Result can be interpreted like major cross match.
- **Called minor** because:
  - ✓ Any Ab in the donor's serum will be **diluted** by the large volume of the recipient's blood.
  - ✓ The Ab may also be **neutralized** by ABH substances present in a recipient's tissues, so is unlikely to cause a serious reaction.
  - ✓ The destructed RBCs of the patient may be **compensated** by the transfused RBC of the donors

Table; Blood group compatibility for transfusion (✓ → compatible, x → incompatible)

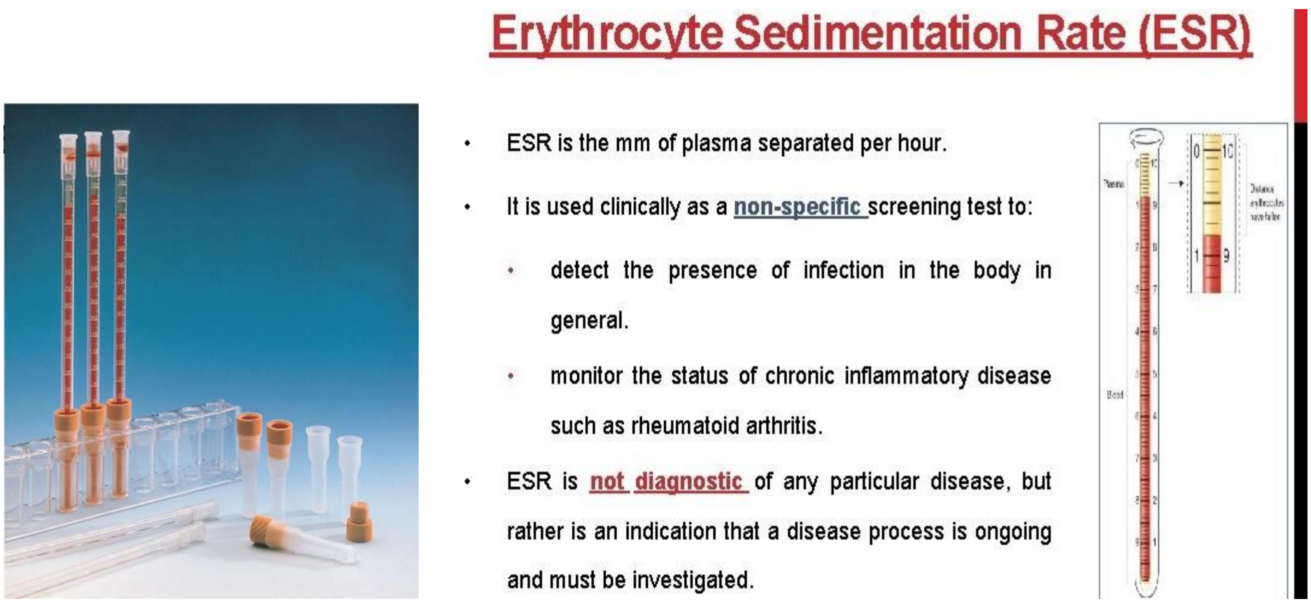


Recipient[1]	Donor[1]							
	O-	O+	A-	A+	B-	B+	AB-	AB+
O-	✓	✗	✗	✗	✗	✗	✗	✗
O+	✓	✓	✗	✗	✗	✗	✗	✗
A-	✓	✗	✓	✗	✗	✗	✗	✗
A+	✓	✓	✓	✓	✗	✗	✗	✗
B-	✓	✗	✗	✗	✓	✗	✗	✗
B+	✓	✓	✗	✗	✓	✓	✗	✗
AB-	✓	✗	✓	✗	✓	✗	✓	✗
AB+	✓	✓	✓	✓	✓	✓	✓	✓

For more, refer under miscellaneous section of Nitsibin short case (click here → Blood Transfusion)

10.1.6 ESR (Erythrocyte Sedimentation Rate) (Macro and micro /µ/ ESR)

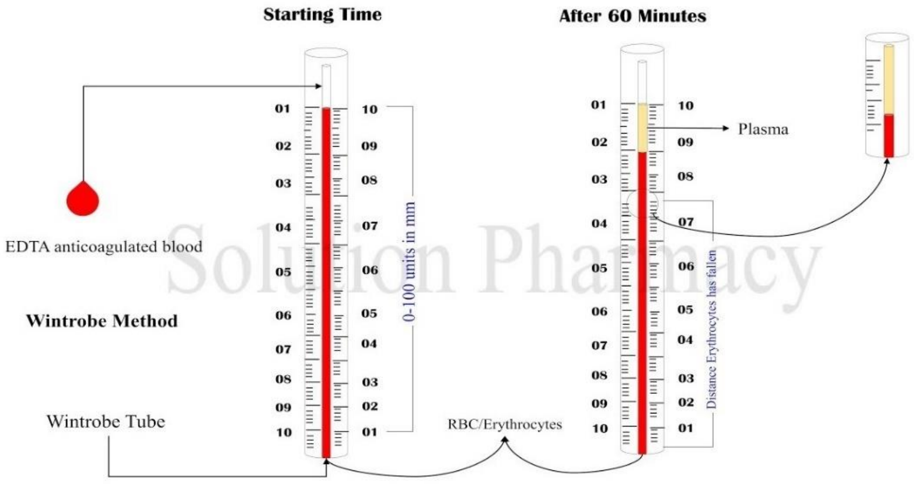
- Sample should be collected with CBC bottle (ESR needs much volume of blood than CBC)
- When whole blood is placed in a vertical tube, red cells will tend to fall toward the bottom.
- The length of fall of erythrocyte in a given interval of time is called ESR
- ESR is used to follow up patients and supportive for some disease diagnosis. But it has no specific diagnostic value
- Has 3 stages
  1. Roulaex formation = 1st 10 minutes
  2. Sedimentation = next 40 minutes
  3. Packing of sediments = last 10 minutes



Erythrocyte Sedimentation Rate (ESR)

- ESR is the mm of plasma separated per hour.
- It is used clinically as a non-specific screening test to:
    - detect the presence of infection in the body in general.
    - monitor the status of chronic inflammatory disease such as rheumatoid arthritis.
- ESR is not diagnostic of any particular disease, but rather is an indication that a disease process is ongoing and must be investigated.

Plasma
Blood
Distance erythrocytes have fallen


Starting Time
After 60 Minutes
EDTA anticoagulated blood
Wintrobe Method
Wintrobe Tube
01 02 03 04 05 06 07 08 09 10
10 09 08 07 06 05 04 03 02 01
0-100 units in mm
Plasma
RBC/Erythrocytes
Distance Erythrocytes has fallen

Pictures; Diagrammatic view of ESR determination

Micro /µ/ ESR[29]

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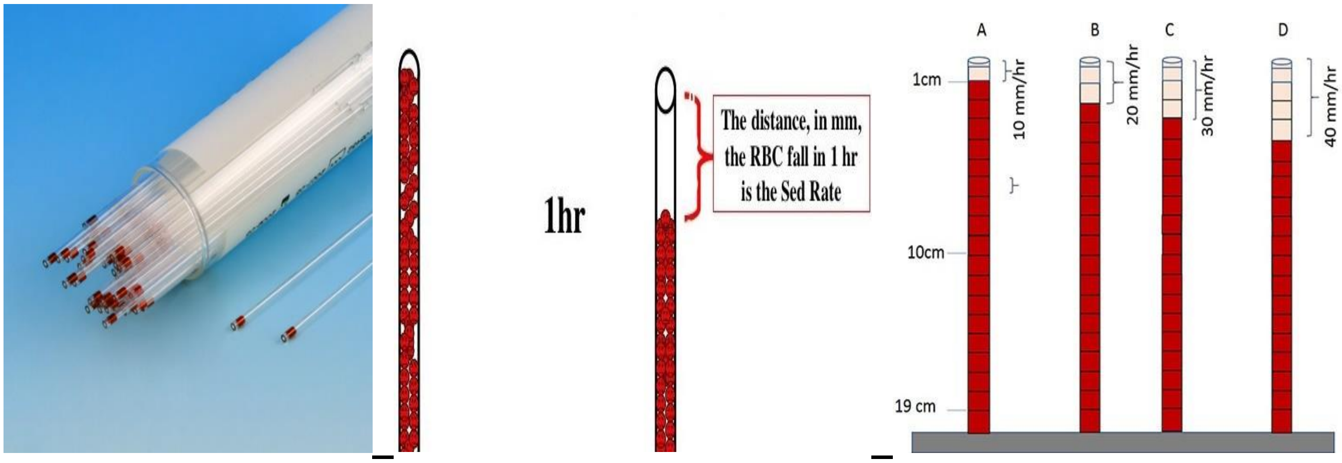
[29] µESR is a routine investigation [especially for neonates} which can be done at bedside by any personnel.



Pictures; µESR determination at bedside

1. Take sample through the red mark of capillary tube
2. Put the tube vertically and mark the end point (top level) of sample filled with blood
3. Check the result after 01 hour and measure the distance in which the blood sample falls down from the initial maximum mark. For the picture in the right, µESR is 10mm/hr, 20mm/hr, 30mm/hr and 40mm/hr for samples of A, B, C and D respectively.

10.2 RBS, FBS, OGTT, and HbA1c

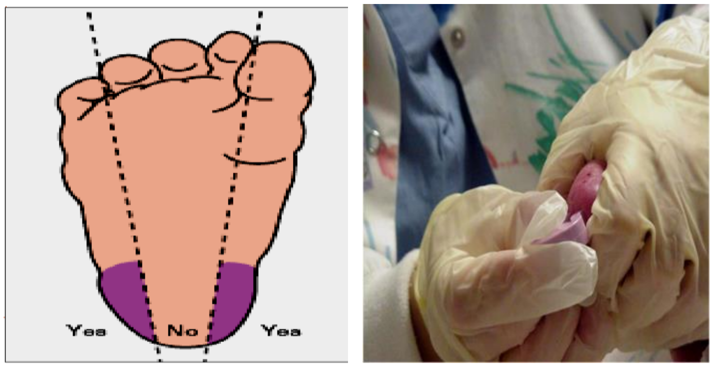
- **RBS** → determining serum glucose level irrespective of food intake or not (but they should have taken food at most less than 8 hours before)
- **FBS** → Fasting is defined as no caloric intake for at least 8 hours
- **OGTT**→ test should be performed (as described by the WHO), using a glucose load containing the equivalent of 75-gram anhydrous glucose dissolved in water. Then measure glucose level after 2 hrs of taking 75-gram glucose (in our set up we use 9 vials of D40, since 1vial of D40 is 8gram, which means 8 x 9 = 72gram)
- **HbA1c** → determines glucose control level for the past 3 months, this is because of 3 month life span of RBC

Put one drop of capillary prick blood sample over the tip of the strip, and read the result (automatic numbers as shown in the picture). If RBS is > 600mg/dl, glucometer failed to interpret and it displays ''H'' instead of numbers meaning ''High''

114
MAYBE?
WONDER
92
19. 10 20:00
mg/dL
Glucometer Elite XL
On Call Plus
M
S

Picture; glucometers

Picture; finger prick for RBS sample collection (also for manual hematocrit sample collection in adults), then draw sample with capillary tube to send for laboratory (only few sample is needed, if glucometer is available in the ward/OPD, you can take directly from fingertip to the test strip and no need of capillary tube.)



Pictures; left) The areas of the foot of a baby or infant that are suitable for obtaining capillary blood. Right) Heel Prick

10.3 U/A (Urine analysis)

Urine examination includes the following

1. Gross /Macroscopic/ examination
2. Chemical Analysis (Urine Dipstick)
3. Microscopic Examination

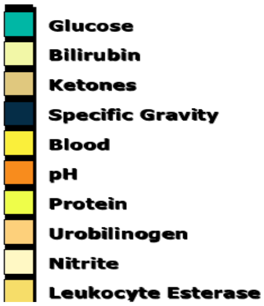
1) Gross /Macroscopic/ examination of urine

- **Odor:** normal urine has aromatic odor
- **Color:** urine has different colors that can be associated with different pathological situations
    - Watery to yellow → normal
    - Deep yellow → concentrated urine
    - Red, tea/ coca colored → hematuria
    - Pussy → pyuria, infected urine
- **Turbidity:** may indicate the presence of crystals, cells, protein
- **Transparency:** freshly voided urine specimen is normally clear and transparent
- **Volume:** The 24-hour urine voided by a healthy adult range from 600 to 2000ml
- **Oliguria:** urine volume is less normal <400ml per 24 hours for prolonged period
- **Diuresis:** temporal increment of urine due to excessive fluid intake
- **Polyuria:** consistent elimination of an abnormally large volume of urine, over 2000ml/24hr.
- **Anuria:** is the nearly complete absence of urine formation

I. Chemical Analysis (Urine Dipstick)

Urine dip stick

ACON
Urinalysis Reagent Strips


Glucose
Bilirubin
Ketones
Specific Gravity
Blood
pH
Protein
Urobilinogen
Nitrite
Leukocyte Esterase

Urine Reagent
TESTS AND READING
Leukocytes
120s
Urobilinogen
60s
Bilirubin
60s
Blood
60s
Nitrite
60s
pH
30s
Specific Gravity
45s
Protein
30s
Glucose
60s
Ketone
60s
PROCEDURE AND
1. Immerse the reagent strip into the urine for approximate 2 seconds, then remove the excess urine on the edge of the container.

10V
ent Strips
For professional
Do not use test
If you have any please contact
Hemolysis
(Any pink coloration)
NOTES
Compare the colors on the reagent areas with the corresponding color chart on the label.

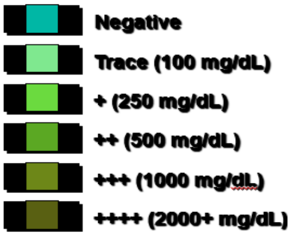
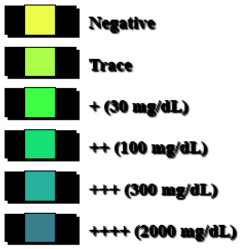
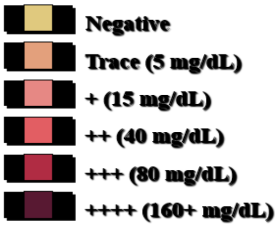
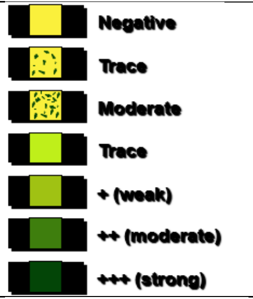
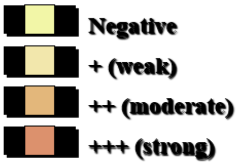
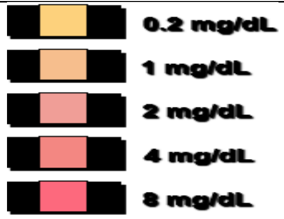
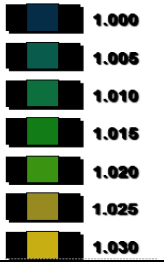
Procedure of urine dip stick

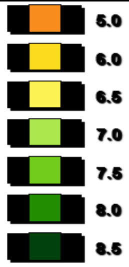
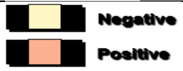
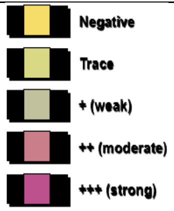
I. Immerse the reagent strip into the urine for up to 2 seconds then remove the excess urine on the edge of the container

II. Compare the colors on the reagent area with corresponding color chart on the container label

III. Report the result

Urine dipstick interpretation

Parameter	Image (report)	Significance
Glucose	 Negative Trace (100 mg/dL) + (250 mg/dL) ++ (500 mg/dL) +++ (1000 mg/dL) ++++ (2000+ mg/dL)	✓ DM ✓ renal glucosuria
Protein	 Negative Trace + (30 mg/dL) ++ (100 mg/dL) +++ (300 mg/dL) ++++ (2000 mg/dL)	Proteinuria ✓ Nephrotic sxx ✓ Edema
Ketone	 Negative Trace (5 mg/dL) + (15 mg/dL) ++ (40 mg/dL) +++ (80 mg/dL) ++++ (160+ mg/dL)	✓ DKA ✓ Starvation ketoacidosis
Blood	 Negative Trace Moderate Trace + (weak) ++ (moderate) +++ (strong)	Hematuria 2ry to ✓ Renal calculi ✓ Glomerulonephritis ✓ Primary or secondary Malignancy from GUT
Bilirubin	 Negative + (weak) ++ (moderate) +++ (strong)	Jaundice (direct bilirubin) 2ry to ✓ CLD ✓ Biliary obstruction
Urobilinogen	 0.2 mg/dL 1 mg/dL 2 mg/dL 4 mg/dL 8 mg/dL	High → increased hepatic processing of bilirubin Low → bile obstruction ✓ CLD ✓ Hemolytic disorder
Specific gravity	 1.000 1.005 1.010 1.015 1.020 1.025 1.030	✓ DI

Ph		Acidic < 4.5 Alkaline > 8 ✓ Respiratory or metabolic acidosis ✓ Urolithiasis
Nitrite		Gram -ve bacteruria ✓ UTI
Leucocyte esterase	 Negative Trace + (weak) ++ (moderate) +++ (strong)	✓ UTI ✓ Pyuria ✓ Urolithiasis

II. Microscopic examination of urine

Urine preparation Procedure for microscopic examination

❖ There are different types of specimens for urinalysis

- ✓ **First Morning Specimen → the recommended specimen of choice**. This is due to the fact that it is generally more concentrated because of the amount of time it remained in the bladder.
- ✓ Random Specimen
- ✓ Postprandial specimen
- ✓ 24 hr urine
- ✓ Clean Catch Urine specimen
  - Mid- stream Specimen
  - Catheterization
- ✓ Once the sample of urine has been properly collected: Pour 10 to 15 ml of the well-mixed urine in to a test tube and place it in the centrifuge (the test tube should always be balanced with a second test tube filled with water/another urine sample) of equal volume
- ✓ Centrifuge the sample at low speeds of between 2,000 to 3,000 rounds per minute /RPM/ for about 7 minutes
- ✓ Decant the supernate (to retain about 0.2- 0.5 ml inside the tube)
- ✓ Shake the tube to mix the sediment and supernate retained in the test tube
- ✓ Using a pipette, collect and place a drop of the re-suspended sediment on to a microscopic slide and place a cover slip over the drop for observation

- ✓ Note** If the urine sample is not analyzed within 2 hours after collection, it should be stored for not more than 24 hours (refrigeration).

Microscopic examination and report

- For urine analysis, the sediment should **first be observed under low power field (LPF)** when observing for crystals, casts, squamous cells or other larger objects. When making a report, the number of casts seen under the microscope is usually reported as the number of each type per low power field. Moreover, low power allows for a wider view, which allows for clear observation of the number of casts seen.

- Note** - When observing the slide under low power, low light source should be used. This is because of the fact that too much light would make it more difficult to see he cellular and crystalline elements.
- To observe and identify cells, crystals and bacteria, **high power field (HPF)** is used. In this case, the types of cells will also be described as the number of each type found per the high-power field.

Abnormal findings in urine microscopic examinations *(for normal reference values click here →* Chapter 11; Reference Intervals for Laboratory Tests*)*

Per High Power Field (HPF) (400x)

- > 3 erythrocytes
- > 5 leukocytes
- > 2 renal tubular cells
- > 10 bacteria

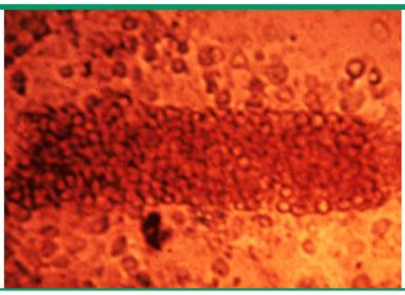
Per Low Power Field (LPF) (200x)

- > 3 hyaline casts
- > 1 granular cast
- > 10 squamous cells (indicative of contaminated specimen)
- Any other cast (RBCs, WBCs)

Presence of:

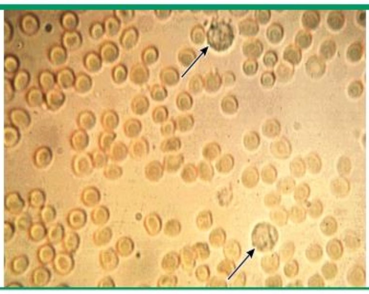
- Fungal hyphae or yeast, parasite
- Pathological crystals (cystine, leucine, tyrosine)
- Large number of uric acid or calcium oxalate crystals

Photomicrograph of urine sediment with a red cell cast



Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis.

Phase-contrast micrograph showing monomorphic red cells in urine sediment



Urine sediment viewed by phase-contrast microscopy showing many red cells and an occasional larger white cell with a granular cytoplasm (arrows). The red cells have a uniform size and shape, suggesting that they are of nonglomerular origin.

10.4 S/E (stool examination)

- For S/E, Collect the sample in a clean, water-tight dry urine free container with a tight lid.
- In the case of neonates and Infants, collect from the diaper.

Saline and iodine Direct wet mount preparations:

1) Saline wet preparation:

- Take one drop of 0.85% saline.
- Take a small amount of stool and mix well.
- The smear should be thin so that you can see the newsprint under the slide.
- Put cover glass and see under the microscope 10x and 40x objective.
  - ✓ This is best to see helminth eggs, larva, and trophozoites.

I. Iodine wet preparation → a.k.a wet preparation.

- Prepare Lugol's iodine solution
  - ✓ Iodine solution consists of:
    - Potassium iodide (KI) = 10 grams
    - Iodine powder crystals = 5 grams
    - Distilled water = 100 ml
  - ✓ Procedure to make Lugol's iodine solution:
    - Dissolve KI in Distilled water.
    - Slowly add iodine crystals.
    - Shake the solution gently until they dissolve.
    - Filter the solution before use, and this is the stock solution.
    - Dilute the stock solution 1:5 with Distilled water. Make this working solution before use.
    - Too weak iodine solution; in that case, organisms will not stain properly.
    - Too strong iodine solution will clump the stool.
  - ✓ Take a drop of Lugol's iodine solution.
  - ✓ Take a small amount of stool and mix it well.
  - ✓ Make a thin smear.

- ✓ Put the cover glass on it and gently press it to get an evenly thin smear.
- ✓ See under 10x and 40x objective lenses.

Concentration methods

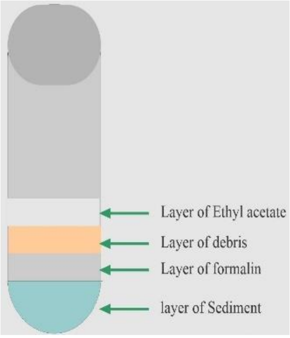
- ❖ The main aim of the concentration method is to remove the debris. Also, when the parasite is low in number
- ❖ There are three methods used for the concentration of stool:
  - ✓ **Formalin-ethyl-acetate concentration method.**
  - ✓ **Zinc-floatation method.**
  - ✓ Sheather sugar floatation method.

I. The formalin-ethyl-acetate concentration:

- ❖ It is the most commonly used concentration method.
- ❖ This method recovers the helminth eggs and larvae, to a lesser extent, trophozoites.
- ❖ Principle → This is based on specific gravity. After centrifugation, the stool's parasites are heavier and settles down at the bottom as sediments. Debris is lighter and rises to the upper layers.
- ❖ Advantages are:
  - ✓ It is easy to prepare the solution an also the procedure is easy to perform.
  - ✓ Inexpensive
  - ✓ There is a rare distortion of parasite forms (eggs).

The procedure of formalin-ethyl-acetate concentration:

- ❖ The stool should be fixed in formalin for at least 30 minutes.
  - ✓ Take 2 to 5 grams of the stool and mix thoroughly in the 10% formalin.
- ❖ Filter the above stool in the formalin.
  - ✓ This can be done by two layers of gauze or a wire screen and collect around 3 ml.
- ❖ Add 10 to 12 mL of 0.85% saline and mix it well.
- ❖ Centrifuge for 2 minutes at 2000 RPM (or2500 RPM).
- ❖ Discard the supernatant and leave 1 to 1.5 mL of the sediment.
  - ✓ If the supernatant is cloudy, then repeat the above steps of saline.
- ❖ Add 9 mL of 10% formalin to the sediment.
- ❖ Now add 3 mL of ethyl acetate.
- ❖ Cap the test tube and shake well for 30 seconds.
- ❖ Centrifuge the tubes for 1 minute at 2000 RPM
- ❖ Four layers will form. The bottom is the sediment that is needed to prepare the smear.

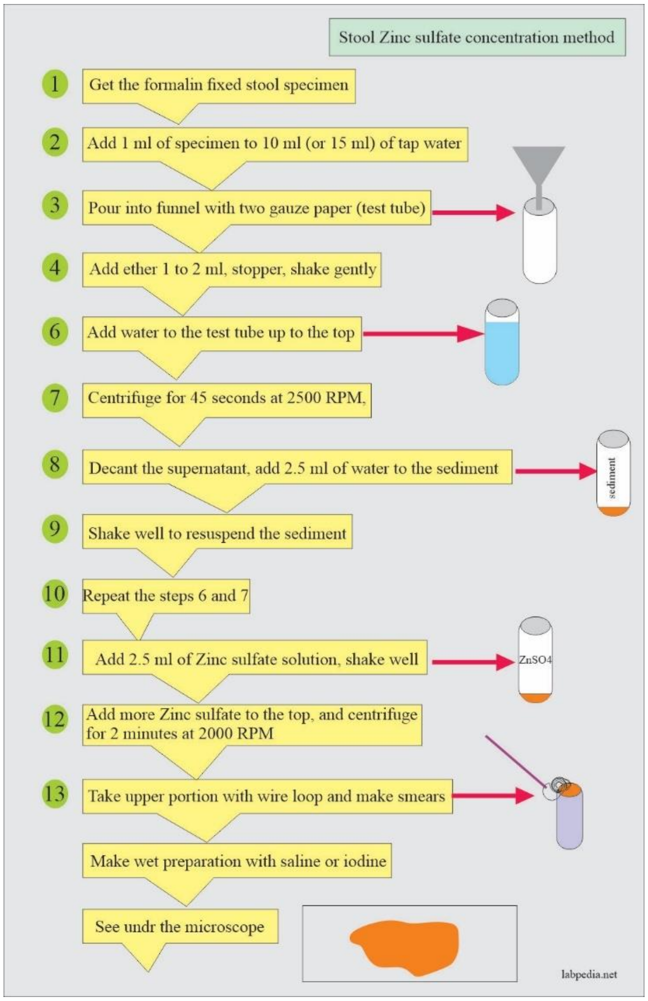


picture; stool formalin ethyl acetate after centrifugation

- Remove the debris with a wooden applicator stick. Decant the upper three layers carefully and leave the sediments in the test tube.
- Clean the sides of the test tube with a swab.
  - ✓ Giardia cyst may stick to the side of the test tube.
- Add a few drops of the formalin and mix the sediment thoroughly. This will preserve the sediment.
  - ✓ Now, we can make the smears in saline and iodine wet preparation.
- Examine under the microscope.

G) Zinc sulphate Floatation Method:

- Some authors believe it a superior method for concentration and identifying eggs and protozoan cyst.
- The parasites are lighter and float on the surface, while the debris settles at the bottom.
- Look at the procedure in the diagram below



Stool Zinc sulfate concentration method

1 Get the formalin fixed stool specimen

2 Add 1 ml of specimen to 10 ml (or 15 ml) of tap water

3 Pour into funnel with two gauze paper (test tube)

4 Add ether 1 to 2 ml, stopper, shake gently

6 Add water to the test tube up to the top

7 Centrifuge for 45 seconds at 2500 RPM,

8 Decant the supernatant, add 2.5 ml of water to the sediment

9 Shake well to resuspend the sediment

10 Repeat the steps 6 and 7

11 Add 2.5 ml of Zinc sulfate solution, shake well

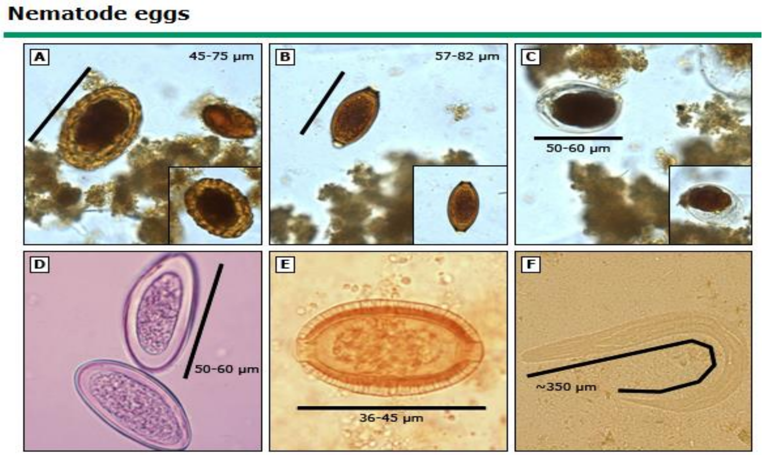
12 Add more Zinc sulfate to the top, and centrifuge for 2 minutes at 2000 RPM

13 Take upper portion with wire loop and make smears

Make wet preparation with saline or iodine

See undr the microscope

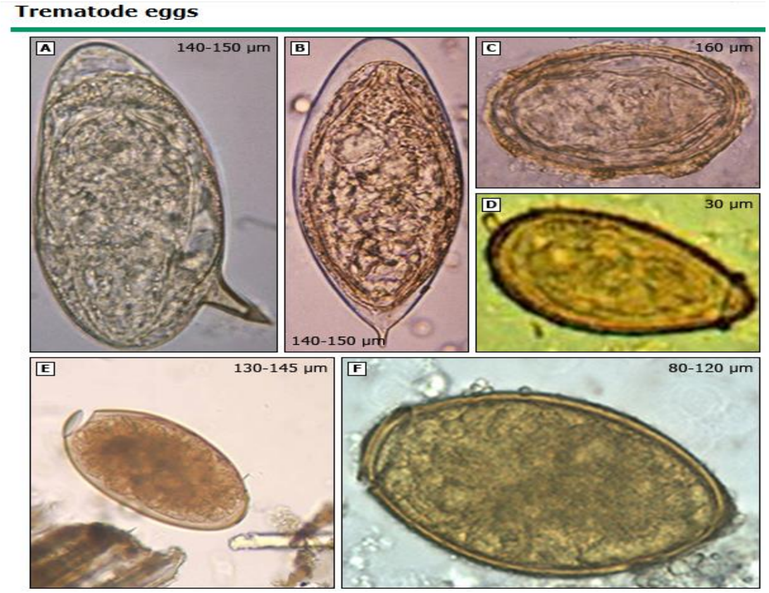
Microscopic images of selected Intestinal parasites



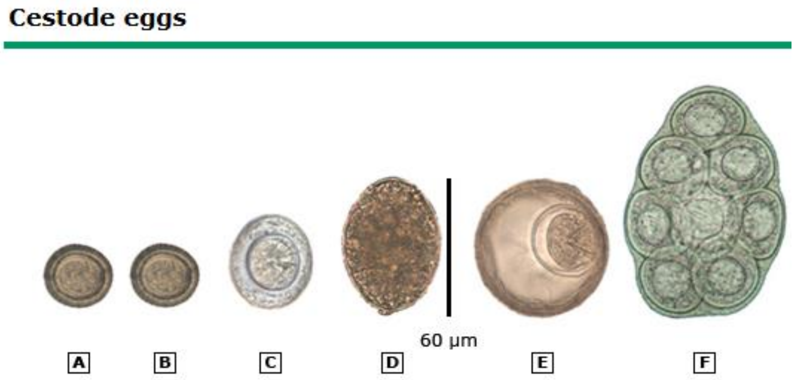
Picture; **Common nematode eggs and larvae** easily recognized on microscopy (wet mount) include: **(A)** ***Ascaris*****, (B)** ***Trichuris*** /wet mount with iodine/, **(C) hookworm** (wet mount with iodine), **(D)** ***Enterobius*** **(pinworm),** (E) *Capillaria*, **(F)** ***Strongyloides*** rhabditiform larvae.

Ascaris eggs are large with rough surfaces and a dark dense center (A). *Trichuris* eggs have distinctive mucus plugs at either end as well as a "tea tray" appearance (B). Hookworm eggs are optically clear at the edges with a dense center composed of one or

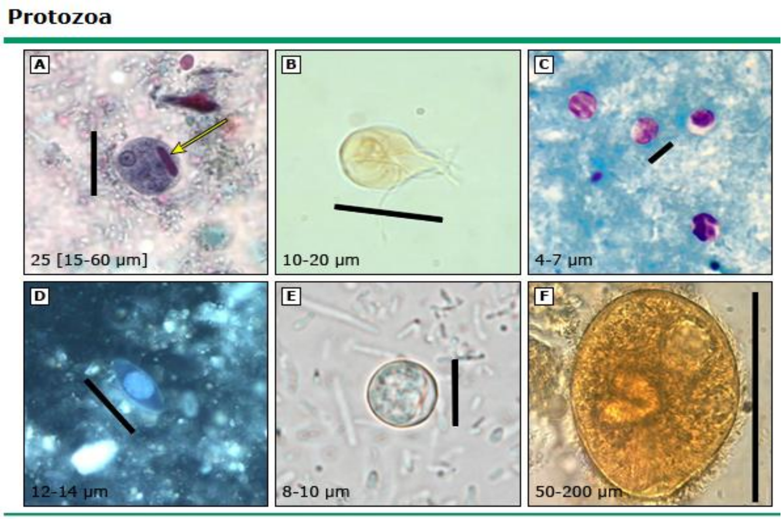
more cells (C). *Enterobius* eggs have a distinctive oval shape with slight concavity (D). *Capillaria* eggs are similar to *Trichuris* but are smaller with more flattened ends (E). *Strongyloides* larva may be distinguished from hookworm larva by the presence of short buccal cavity and primordial genitalia midway down the body (F).
The measurements given represent the range seen for the black bar lengths for each organism.



Picture; **Common trematode eggs** seen on easily recognized on microscopy (wet mount with iodine) include: **(A) *Schistosoma mansoni*, (B) *Schistosoma haematobium*, (C) *Schistosoma japonicum***, (D) *Clonorchis*, (E) *Fasciola*, (F) *Paragonimus*
Schistosoma eggs are the largest of the helminths and can be distinguished by their spines which are lateral (*S. mansoni*, A), terminal (*S. haematobium* and *S. intercalatum*, B), or vestigial (*S. japonicum* or *S. mekongi*, C). *Clonorchis* and *Opisthorchis* eggs have an operculum and small remnant at the opposite end (D). *Fasciola* and *Fasciolopsis* are also operculated but smooth (E). *Paragonimus* eggs are also operculated but have a thick, almost pointed opposite end (F).
The measurements given represent the length of the eggs along the long axis for each organism.



Picture; **Common cestode eggs** recognized on wet mount include: (A) ***Taenia solium*, (B) *Taenia saginata*, (C) *Hymenolepis nana*, (D) *Diphyllobothrium latum***, (E) *Hymenolepis diminuta*, (F) *Dipylidium caninum.*
The eggs can be useful for diagnosis, although the primary diagnostic forms are the mature (gravid) proglottids and the scolex. The eggs of *Taenia* are indistinguishable (A and B).



Picture; **Common protozoa** easily recognized on microscopy include: (A) ***Entamoeba histolytica*** (trichrome stain), (B) ***Giardia lamblia*** (wet mount), (C) *Cryptosporidium* (acid-fast stain), (D) *Cystoisospora* (wet mount with exposure to ultraviolet light), (E) *Cyclospora* (wet mount), (F) *Balantidium coli* (wet mount with iodine).
E. histolytica may appear as a cyst form with chromatid bar (A). *Giardia lamblia* has distinctive flagella (B). *Cryptosporidium* is small with acid-fast staining (C). *Cystoisospora* (formerly *Isospora*) has an oblong shape, one or two nuclei, natural fluorescence, and acid-fast positivity (D). *Cyclospora* is similar to but larger than *Cryptosporidium*, with natural fluorescence and acid-fast positivity (E). *Balantidium coli* is the largest protozoan infecting humans and the only ciliate (F).
The measurements given represent the range seen for the black bar lengths for each organism.

For more images, look at investigation part of intestinal infection section of Nitsbin short cases (click here → Amoeba (አሜባ), Giardia (ጃርዲያ), Intestinal Helminthic Infestations (የአንጀት ጥገኛ ተውሳክ ፣ የአንጀት ትላትል) *and blood flukes*)

10.5 Serology and Rapid diagnostic tests /RDT/

10.5.1 Urine HCG[30]

- Detect the presence of Human chorionic gonadotrophin (HCG) hormone, which is produced by the trophoblastic tissue in the placenta
- HCG has two sub units: The α sub unit & the β subunit
- It has certain **importance** such as: **To confirm pregnancy**, to diagnose **ectopic pregnancy** and **GTD and trophoblastic tumors, testicular cancer in males.**
- **Serum HCG reaches detectable level within 24 hours after implantation**.

Methods of evaluation

9) Strip test → common in our set up

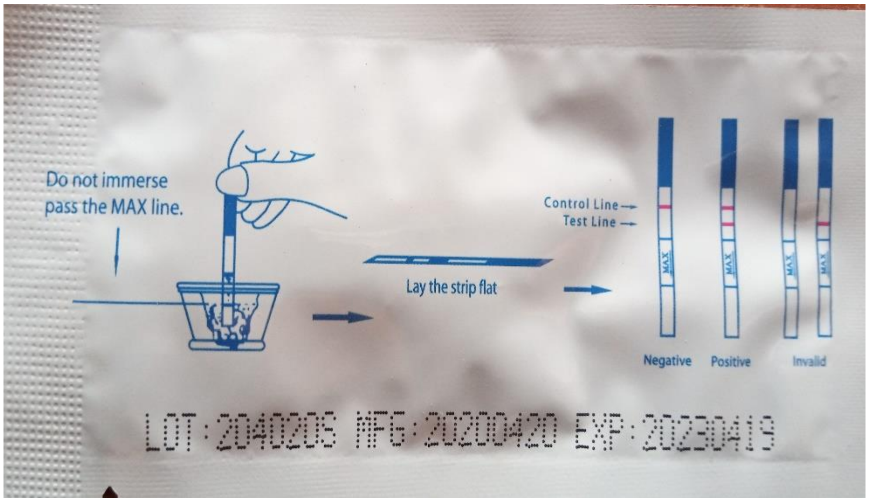
- Principle:

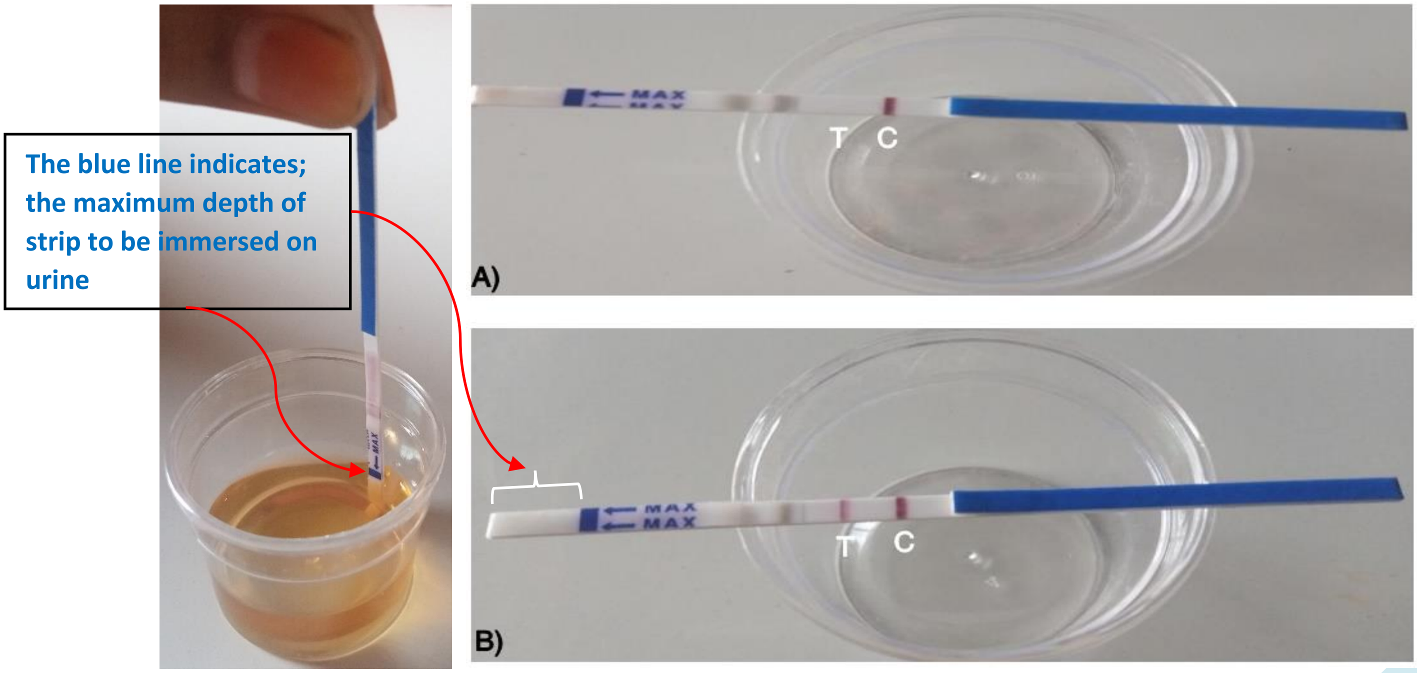
---

[30] Urine HCG [strep test] is very simple test which can be performed at bedside (request ''urine HCG kit'' and do it by yourself instead of sending sample to lab, which decreases time wastage)

  - The test reaction is between the HCG in the urine and gold coated antibody on the strip.
  - A positive control is also impregnated on the strip so that interpretation will be very easy.
  - The preferential sample for HCG test is first morning urine

- Steps and Result interpretation → look at the images below
  - Immerse the strip on the urine sample up to the maximum line (horizontal blue line)
  - Lay the strip flat (you can put on the top of urine cup)
  - Read the result within 5 minutes
    - **Double lines (control and test) → positive for HCG.**
    - **Control line only → Negative for HCG**
    - **Invalid result → without having any line or appearance of test line only.**


Do not immerse pass the MAX line.
Lay the strip flat
Control Line
Test Line
MAX
Negative
Positive
Invalid
LOT:2040205 MFG:20200420 EXP:20230419


The blue line indicates; the maximum depth of strip to be immersed on urine
MAX
T
C
A)
B)

Picures; Urine HCG strip test; A) negative urine HCG test in which only the control (C) line is visible; B) shows positive urine HCG test in which both control (C) and test (T) line are visible. *Picture taken, from two patient samples, at private clinic in Ethiopia.*

10) Direct agglutination slide test (direct latex slide test)

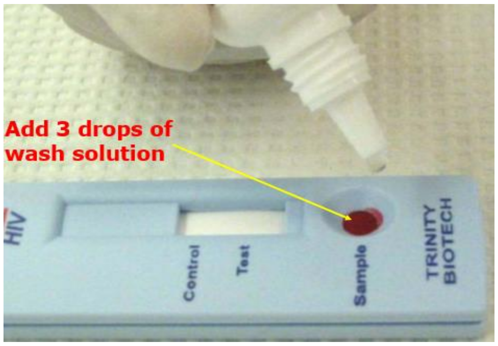
- Principle:
    - Latex reagent coated with anti-HCG antibodies + urine
    - Presence of visible agglutination positive for HCG.
    - No visible agglutination indicates Negative for HCG

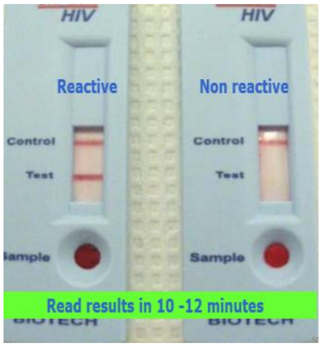
11) Indirect agglutination slide test

- Principle:
    - Urine + anti-HCG antibody + latex HCG
    - Presence of visible agglutination negative for HCG.
    - No visible agglutination indicates positive for HCG

10.5.2 PICT

- A rapid test which was previously known as **provider-initiated counselling and testing (PICT). Current recommendation is test and then counsel, so the name changed as provider-initiated testing and counselling.**
- An antigen is coated on the strip with positive control.
- up on addition of serum /plasma or whole blood depending on the test procedure, there will be reaction between antigen and antibody if present in the sample.
- **Reactive results: two colored bars** (one for the control & the other for the patient)
- **Non- reactive: single colored bar (positive control only)**
- **Invalid result: without having any line.**


Add 3 drops of wash solution
HIV
Control
Test
Sample
TRINITY BIOTECH


HIV
HIV
Reactive
Non reactive
Control
Test
Control
Test
Sample
Sample
Read results in 10 -12 minutes
BIOTECH
BIOTECH

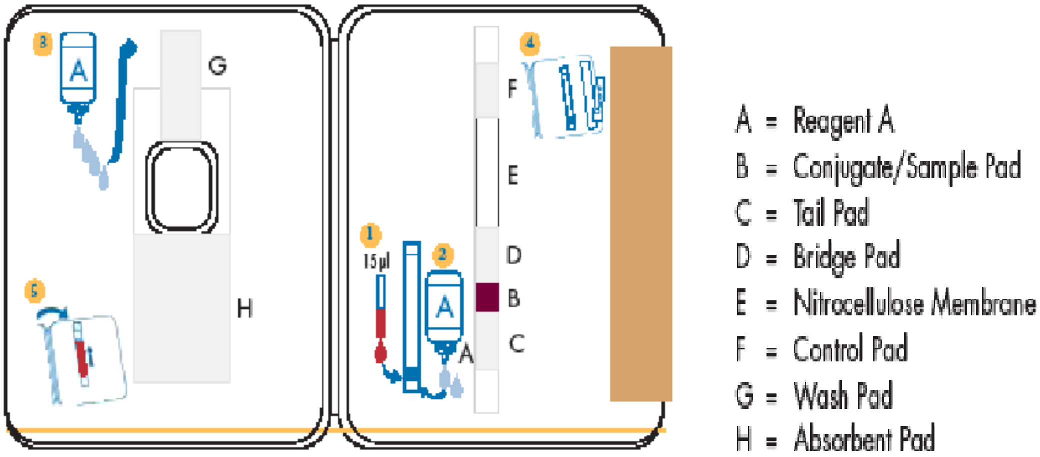
For final result interpretation look at investigation section of RVI from long case of Nitsibin (click here → Chapter 5; RVI (ኤችአይቪ ኤዲስ))

10.5.3 Rapid malaria test

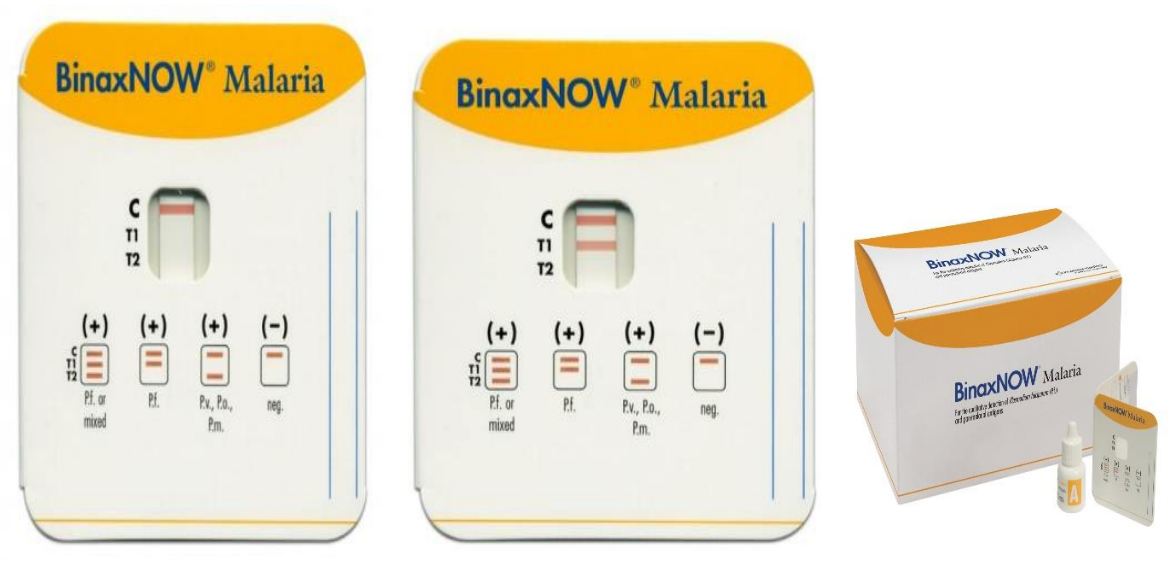
- A 15-minute test which detects circulating malaria antigens in whole blood.
- The *only* FDA cleared rapid malaria test.
- *Plasmodium falciparum* → Sensitivity 95.3%, Specificity 94.2%
- *Plasmodium vivax* → Sensitivity 68.9%, Specificity 99.8%
- Note: Publications report *P. ovale* as being harder to detect as it only attacks young erythrocytes
- Histidine-rich protein II (HRP II) is specific to *P. falciparum* while aldolase is a pan-malarial agent.
- This Test has monoclonal antibodies directed against these proteins, which detects them in a modified lateral flow format.

Procedure (steps)

- Apply 15 µl of whole blood to the purple pad.
    - Venous or capillary whole blood.
    - EDTA collection tubes.
    - Mylar-coated capillary tubes included in kit.
- Apply 2 drops of Reagent to the white pad below where the blood is applied.
- Apply 4 drops of Reagent to the pad located at the top of the left side of the test device.
- Close the device and read in 15 minutes.



A = Reagent A
B = Conjugate/Sample Pad
C = Tail Pad
D = Bridge Pad
E = Nitrocellulose Membrane
F = Control Pad
G = Wash Pad
H = Absorbent Pad


BinaxNOW® Malaria
C
T1
T2
(+)
(+)
(+)
(-)
P.f. or mixed
P.f.
P.v., P.o., P.m.
neg.

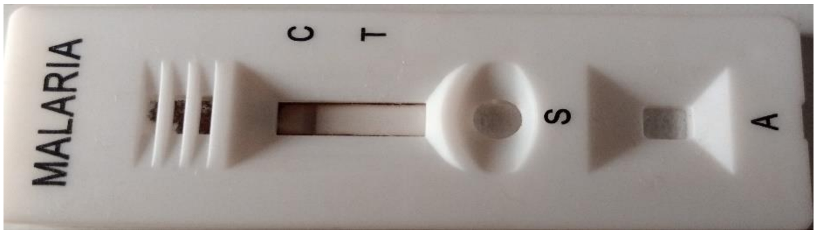
Immage; **Rapid malaria test;**

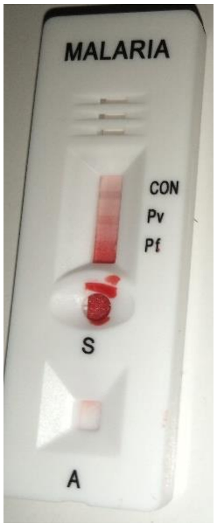
A) T1 Positive → Positive result for P. falciparum (P.f.)

B) T2 Positive → Positive result for P. vivax (P.v.) or P. malariae (P.m.) or P. ovale (P.o.) In some cases the appearance of only the T2 Line may indicate a mixed infection with two or more of P.v., P.m., and P.o.

C) T1 + T2 Positive → Positive result for P. falciparum (P.f.) In some cases the appearance of both the T1 and T2 Lines may indicate a mixed infection of P.f. with another species,

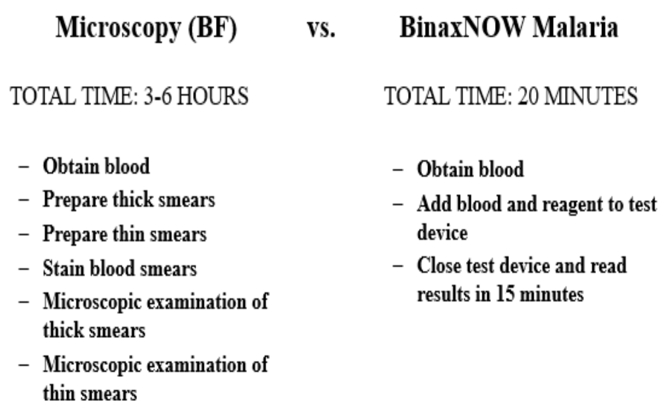
D) No T1 or T2 Lines → Negative result (no malaria antigens were detected)


MALARIA
C
T
S
A


MALARIA
CON
Pv
Pf
S
A

MALARIA
CON
Pv
Pf
S
A

Pictures; RDT for malaria test; pf = P. Falciparum, pv = P. vivax, CON = control, S = place for sample, A = place for buffer. *Picture taken, from a patient sample, at private clinic in Ethiopia.*



Microscopy (BF) vs. **BinaxNOW Malaria**

TOTAL TIME: 3-6 HOURS

- Obtain blood
- Prepare thick smears
- Prepare thin smears
- Stain blood smears
- Microscopic examination of thick smears
- Microscopic examination of thin smears

TOTAL TIME: 20 MINUTES

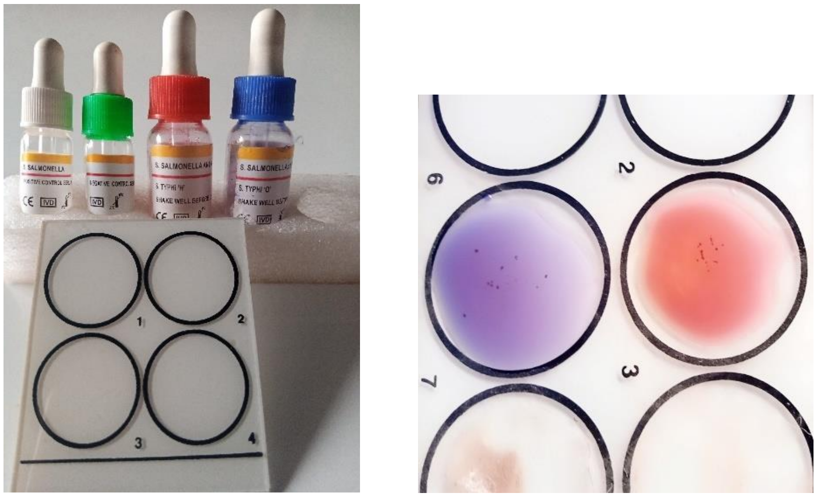
- Obtain blood
- Add blood and reagent to test device
- Close test device and read results in 15 minutes

10.5.4 widal test

- Measures agglutinating antibodies to O and H antigens of salmonella typhi from serum
- The minimal titers defined as positive for the O (surface polysaccharide) antigens for active infection and H (flagellar) antigens in past infection or in immunized person.
- Steps;
    - On clean slide, a drop of serum is placed (non-hemolyzed sample)
    - Then a drop of antigen suspension is added
    - Finally mix, look for agglutination
- Widal test may be used as an adjunt to diagnosis in the proper clinical setup particularly in children < 10 years old and travellers from nonendemic areas.
- The Widal test is, however, characterized by false positive results. But we are using it currently in our set up
- Limitation of widal test
    - **False positive reactions**
        - Due to **past infection**
        - Cross reaction (**malaria, relapsing fever, non-typhoidal salmonella**)
    - **False negative** reaction
        - Early typhoid cases
        - Poor antigen preparation
        - Poor transport of reagents &storage.

S. SALMONELLA
POSITIVE CONTROL SERUM
NEGATIVE CONTROL SE
IVD
S. SALMONELLA ANTI
S. TYPHI 'H'
SHAKE WELL BEFORE
S. SALMONELLA A
S. TYPHI 'O'
SHAKE WELL BEFO

Pictures; widal test reagents; +ve control, negative control, ''H'' antigen and ''O'' antigen. *Picture taken from a private clinic in Ethiopia.*



Pictures; widal test; right) reactive widal test with clear agglutination. *Picture taken, from two patient samples, at private clinic in Ethiopia.*

Widal test - Click on the link below and watch the video
https://youtu.be/dflOQ8hXUbA

N.B Salmonella typhi stool antigen test is very specific and sensitive (up to 99%) than widal test

10.5.5 Weil-Felix slide agglutination test

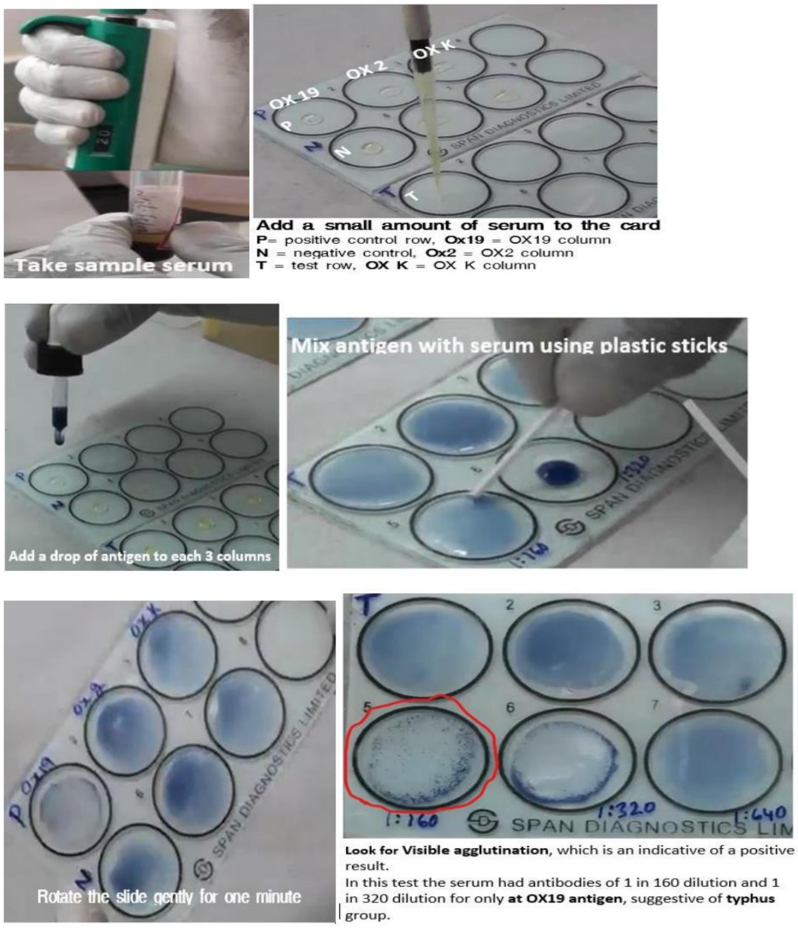
- A Weil-Felix reaction is a type of agglutination test in which patients' serum is tested for agglutinins to O antigen of certain non-motile Proteus and rickettsial strains (OX19, OX2, OXK) to determine the presence and type of rickettsial infection
- OX19, OX2 are strains of Proteus vulgaris. OXK is the strain of Proteus mirabilis.
- The blood serum of a patient with suspected rickettsial disease is tested against certain strains of (OX-2, OX-19, OX-K).
- In 1915, Weil and Felix showed that serum of patients infected with any member of the typhus group of diseases contains agglutinins for one or more strains of O X Proteus.
- In cases of typhus, the reaction usually appears before the 6th day and reaches its height in the second week.

Procedure

- The Weil-Felix Test can be done as either a slide or a tube test. Here we are going to discuss slide test
- The antigens necessary (OX2, OX19, and OXK) can be obtained commercially.
- On a solid surface (glass slide, tile, card), a small amount (50- 100 µL) of the patient's serum is placed.
- A single drop of the desired antigen is added, and the resulting suspension is mixed and then rotated for one minute.
- Visible agglutination is indicative of a positive result, and corresponds roughly to a titre of 1:20.
- Positive results can be further titrated using the tube method, which is more labour- intensive.

Proteus OX19 A
HF-POX195
OX190516-20
5mL
2017-10
IVD
Quality Diagno
SS16
STAINED SUSPENSION
Proteus OX2
Proteus OXK A
HF-POXK5
OXK0516-20
5mL
2017-10
Quality Diag
5 ml
PROGEN
OX19
PROGEN
OX2
PROGEN
OXK

Pictures; reagents for Weil - Felix test (OX 19, OX2 and OX K)



Take sample serum

Add a small amount of serum to the card
P= positive control row, **Ox19** = OX19 column
N = negative control, **Ox2** = OX2 column
T = test row, **OX K** = OX K column

Add a drop of antigen to each 3 columns

Mix antigen with serum using plastic sticks

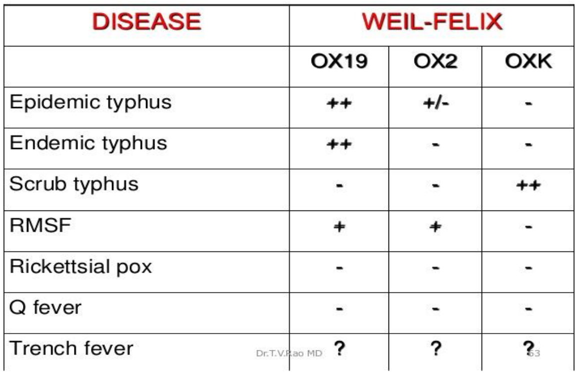
Rotate the slide gently for one minute

Look for Visible agglutination, which is an indicative of a positive result.
In this test the serum had antibodies of 1 in 160 dilution and 1 in 320 dilution for only **at OX19 antigen**, suggestive of **typhus** group.

Pictures; Weil - Felix test procedure

Interpretation of the result

- Look at Agglutination over the slide
- Sera from endemic typhus agglutinate OX19, OX2.
- Tick borne spotted fever agglutinate OX19, OX2.
- Scrub Typhus agglutinate OXK strain
- Test is negative in rickettsial pox, trench fever and Q-fever.
- False positive reaction may occur in urinary or other Proteus infections Test may be negative in 50 % scrub typhus



DISEASE	WEIL-FELIX		
	OX19	OX2	OXK
Epidemic typhus	++	+/-	-
Endemic typhus	++	-	-
Scrub typhus	-	-	++
RMSF	+	+	-
Rickettsial pox	-	-	-
Q fever	-	-	-
Trench fever	?	?	?

Dr.T.V.Rao MD
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Table; Interpretation of Weil - Felix result, RMSF = Rocky mountain spotted fever

Limitations of The Weil-Felix test

- It suffers from **poor sensitivity and specificity,** with a recent study showing an overall sensitivity as low as 33% and specificity of 46%. As a result, it has largely been supplanted by other methods of serology, including indirect immunofluorescence antibody (IFA) testing, which is the gold standard.
- **False negative** reaction is common in **scrub typhus.**
- **False positive may occurs in P**rotues infection, Brucellosis, Borreliosis
- **However, in resource-limited settings (like in our set up), it still remains an important tool in the diagnosis and identification of public health concerns, such as outbreaks of epidemic typhus.**

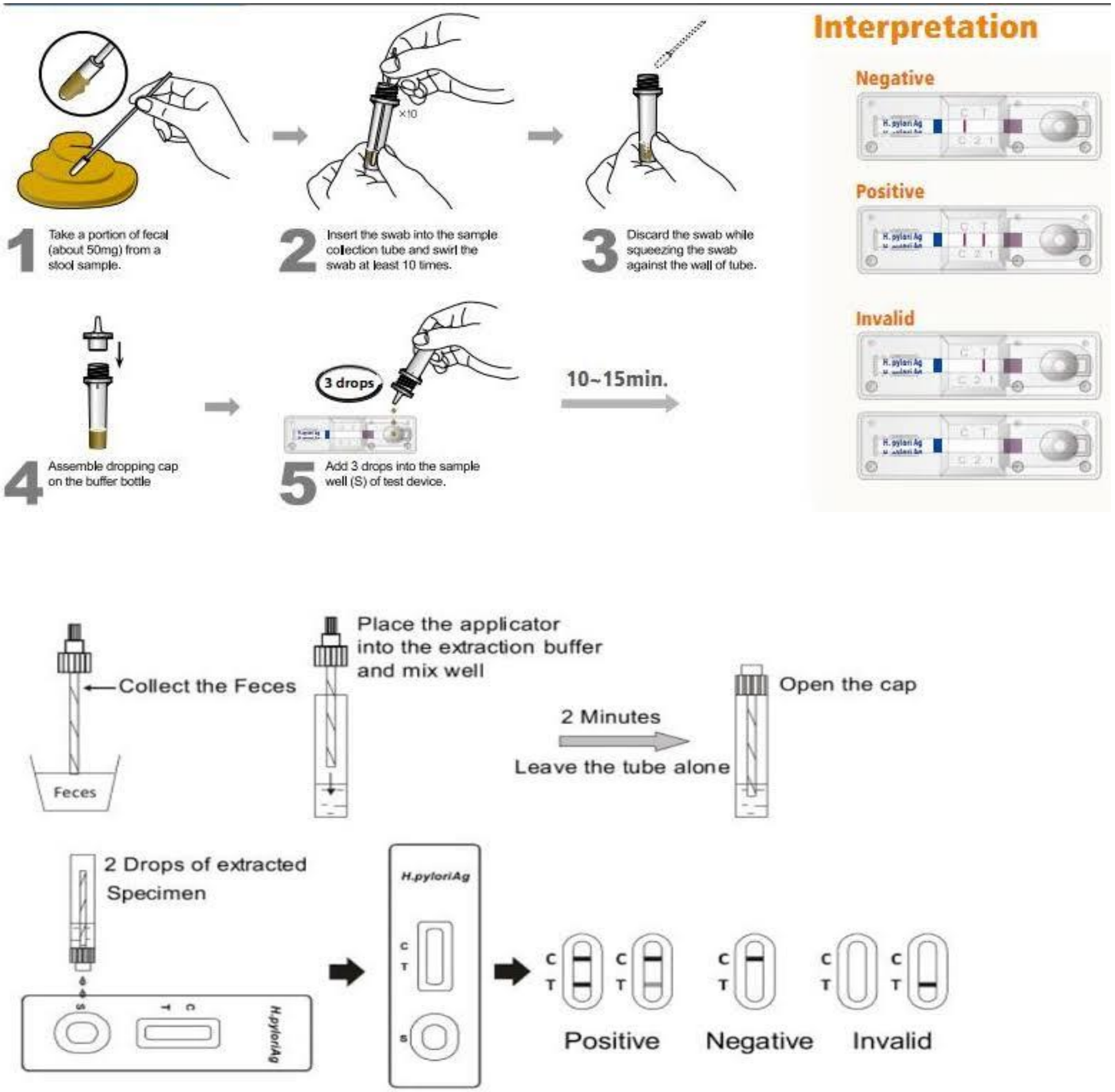
Weil Felix - a slide agglutination test for rickettsial disease
- Click on the link below and watch the video

https://youtu.be/ilqsQWDvggo

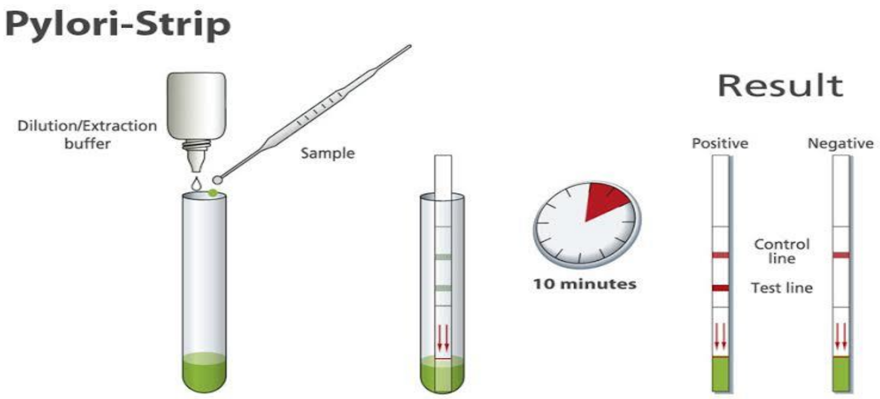
10.5.6 H. Pylori stool antigen and serum Ab test

H.Pylori Antigen
ID
C
T
S
Sample Collection Tube
H.pylori Ag
C
T
ID
S

Pictures; **H. pylori stool antigen kits**


Interpretation
Negative
Positive
Invalid
H. pylori Ag
C T
1 Take a portion of fecal (about 50mg) from a stool sample.
×10
2 Insert the swab into the sample collection tube and swirl the swab at least 10 times.
3 Discard the swab while squeezing the swab against the wall of tube.
4 Assemble dropping cap on the buffer bottle
3 drops
5 Add 3 drops into the sample well (S) of test device.
10~15min.
Collect the Feces
Feces
Place the applicator into the extraction buffer and mix well
2 Minutes
Leave the tube alone
Open the cap
2 Drops of extracted Specimen
S
T C
H.pyloriAg
C
T
S
Positive
Negative
Invalid

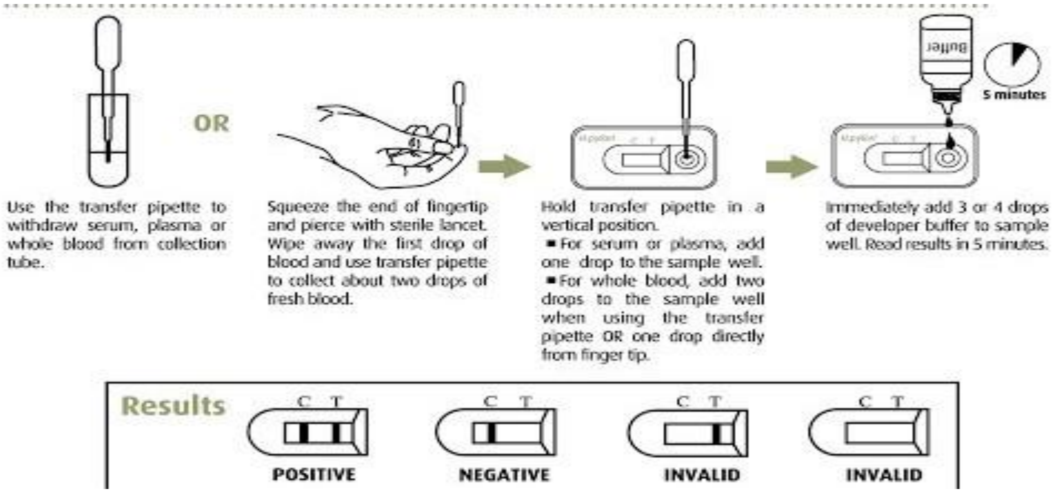
Diagram; steps of **H. pylori antigen stool (fecal) test with kit**; Detects directly the presence of H. pylori antigen in a stool sample. A stool test can detect traces of H. pylori in the feces. This test can be used to diagnose the infection and confirm that it has been cured after treatment. One line = negative (control test), two line = positive, No line = invalid. The absence of the control line, makes the result invalid. In this case, the sample must be retest.


Pylori-Strip
Dilution/Extraction buffer
Sample
10 minutes
Result
Positive
Negative
Control line
Test line

Diagram; **H. pylori antigen stool (fecal) stripes test;** Detects directly the presence of H. pylori antigen in a stool sample. A stool test can detect traces of H. pylori in the feces. This test can be used to diagnose the infection and confirm that it has been cured after treatment. One green line = negative (control test), One green line AND one red line = positive, No line = invalid. The absence of the control line, which is the upper green line, makes the result invalid. In this case, the sample must be retest.

BUFF
tore at 2°C t
H.P Ab
C
T
S

Picture; **H. pylori serum antibody test cassette/kit/**; H. pylori serum antibody test cassette or strips detects antibodies to the bacteria and will not distinguish previous infection from a current one. If test is negative, then it is unlikely that a person has H. pylori infection. If ordered and positive, results should be confirmed using stool antigen or breath test. As a result, blood tests cannot be used to see if the infection has been cured after treatment. *Picture taken from a private clinic in Ethiopia.*


OR
Buffer
5 minutes
Results
C T
POSITIVE
C T
NEGATIVE
C T
INVALID
C T
INVALID

Use the transfer pipette to withdraw serum, plasma or whole blood from collection tube.

Squeeze the end of fingertip and pierce with sterile lancet. Wipe away the first drop of blood and use transfer pipette to collect about two drops of fresh blood.

Hold transfer pipette in a vertical position.
- For serum or plasma, add one drop to the sample well.
- For whole blood, add two drops to the sample well when using the transfer pipette OR one drop directly from finger tip.

Immediately add 3 or 4 drops of developer buffer to sample well. Read results in 5 minutes.

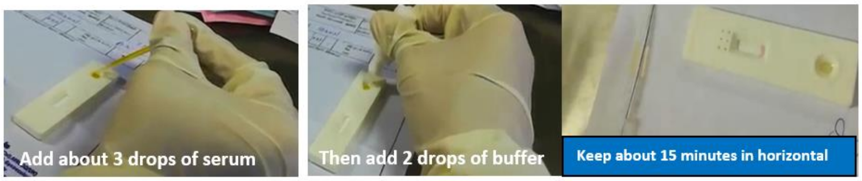
Picture; **H. pylori serum antibody test procedures**

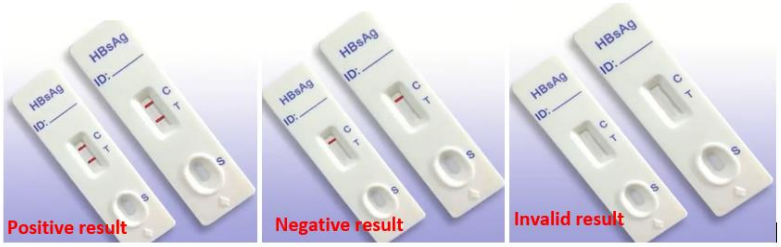
10.5.7 HBsAg (Hepatitis B virus surface antigen) test

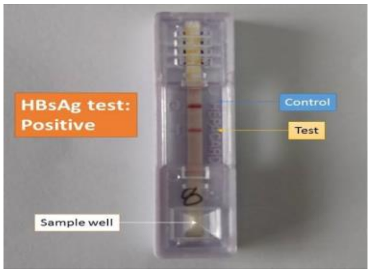
HBsAg
ID:
C
T
S
HBsAg
ID:
C
T
S

Picture; **HBsAg test kit**

HBsAg test procedure and result interpretation


Add about 3 drops of serum
Then add 2 drops of buffer
Keep about 15 minutes in horizontal


HBsAg
ID:
C
T
S
Positive result
Negative result
Invalid result

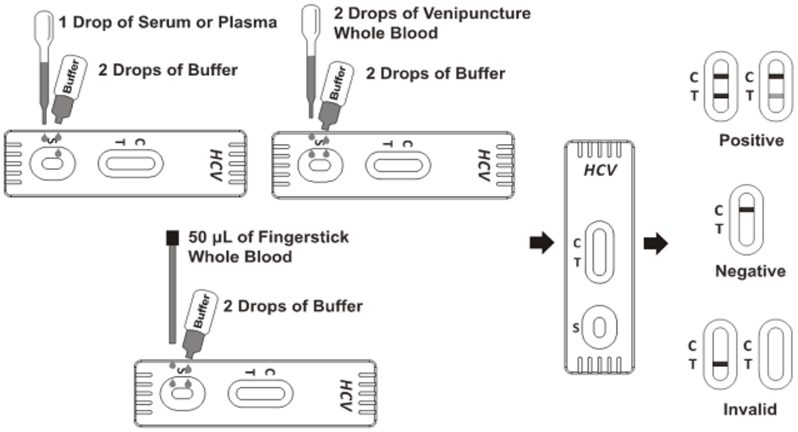

HBsAg test: Positive
Control
Test
Sample well

HepBs Ag test procedure - Click on the link below and watch the video

https://youtu.be/h3iAL26d6SY

10.5.8 HCV Ab (Hepatitis C virus antibody) test

Picture; **HCV antibody test kit**


1 Drop of Serum or Plasma
2 Drops of Buffer
2 Drops of Venipuncture Whole Blood
2 Drops of Buffer
50 µL of Fingerstick Whole Blood
2 Drops of Buffer
Buffer
S
C
T
HCV
Positive
Negative
Invalid

Diagram; **HCV antibody test procedure and result interpretation**

HCV
C
T
Anti-HCV Test
HCV
C
T
S

Picture; **HCV antibody positive test results**

10.5.9 rk- 39 Rapid Diagnostic Test

- **rk- 39 (recombinant kinase 39)** is a Serologic (antibody strip) test for VL
    - **rK39** is a 39-amino acid repeat of a kinesin-related protein cloned from *Leishmania chagasi* and conserved in *L. donovani* complex.
- **it has** 72% to 94 % sensitivity and 67 % to 98 % specificity
    - **More Specific and sensitive** (reach up to 99%) **in non-endemic** area like south east Asia (India)
    - **Not specific in endemic area like east Africa (Ethiopia, Sudan, Kenya)**
- Used for **screening purpose**
- Common and available in Ethiopia.
- Several brands of tests with rK39 antigen are available. The widely available rK39 test in the market include **Kalaazar Detect™ InBios, DiaMed-IT-Leish**, etc.
- So, always read the package inserted carefully and follow the manufacturer's instructions.
- Some brands can be used only with serum, while others can be used with whole blood collected by finger prick
- **Procedure** *(see pictures below);* In general, the test procedure is as follows;
    - Remove the test strip from the pouch and place it on a flat surface.

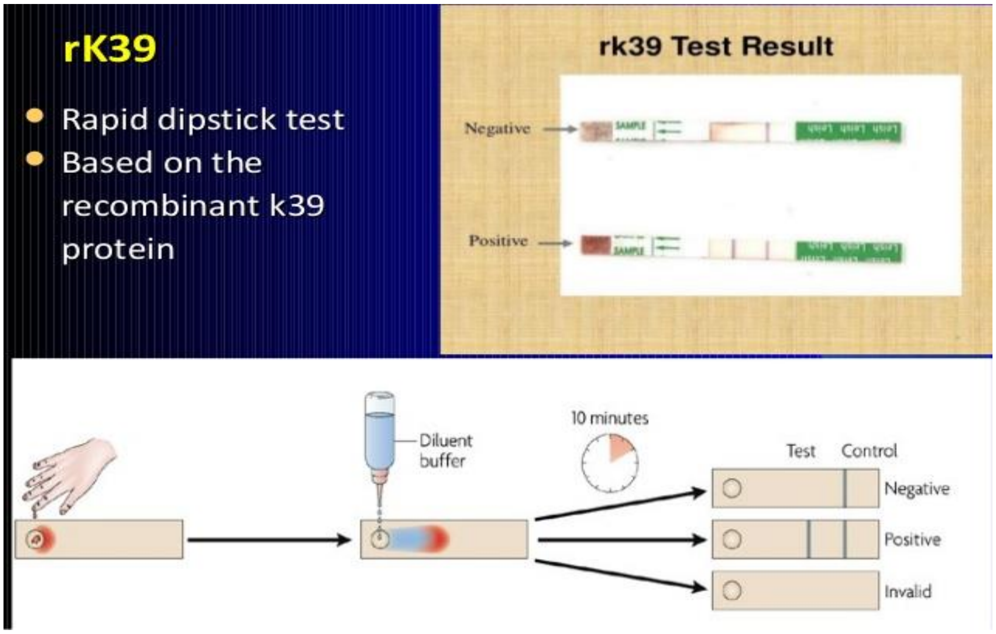
  - Place a specified amount of patient specimen (serum or finger-prick blood) on the absorbent pad on the bottom of the strip.
  - Add the specified amount of buffer provided.
  - Read the result after 10 - 20 minutes according to the manufacturer's instructions.
- **Some brands require a slightly different procedure, for example:**
  - Take a test tube or a U-bottom microtitre plate.
  - Add a specified amount of buffer to the tube or well.
  - Add a specified amount of specimen (blood or serum) to the tube or well and mix.
  - Immerse the test strip into the buffer-specimen mixture.
  - Read the result after 10 - 20 minutes according to the manufacturer's instructions.

Interpretation of the test

- **Positive result:** When **both, control and test lines**, appear, the sample tested has antibodies against recombinant K39 antigen of Leishmania. Even a faint line should be considered positive.
- **Negative result:** When **only the control line** appears, there are no antibodies against recombinant K39 antigen of Leishmania present in the patient's sample.
- **Invalid result:** When **no control line appears**, a fresh patient sample should be tested with a new strip.

Advantages and disadvantages of the rK39 test

- Advantages
  - Simple to perform with minimal training.
  - Does not require a laboratory.
  - Can be performed with finger-prick whole blood, serum or plasma.
  - Kits can be transported and stored at ambient temperature (up to 30 °C).
  - Results are available within 10—20 minutes
- Disadvantages
  - Cannot distinguish between active cases and relapse in previously treated cases. Therefore, interpretation must always be accompanied by clinical case definition.
  - In patients with advanced HIV infection, a negative result does not rule out VL diagnosis.

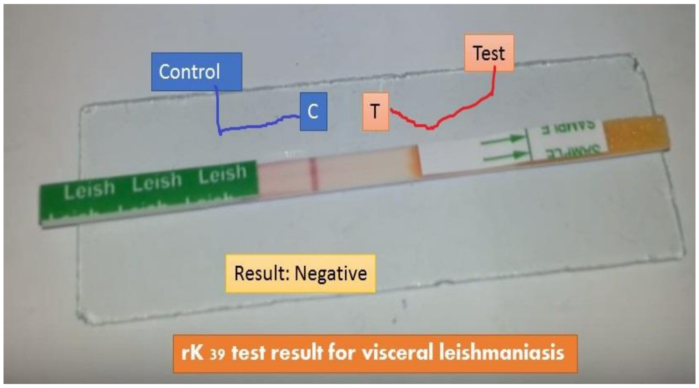


rK39

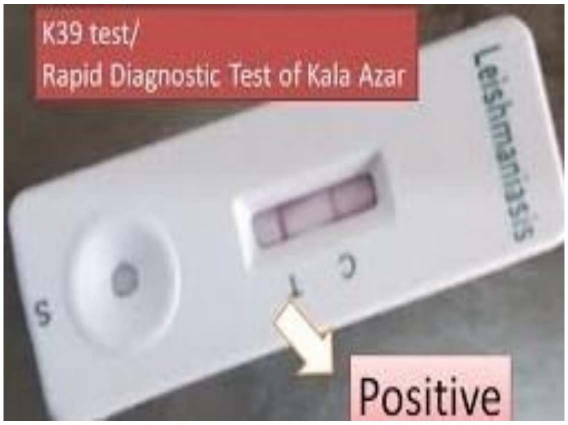
- Rapid dipstick test
- Based on the recombinant k39 protein

rk39 Test Result
Negative
Positive
Diluent buffer
10 minutes
Test
Control
Negative
Positive
Invalid

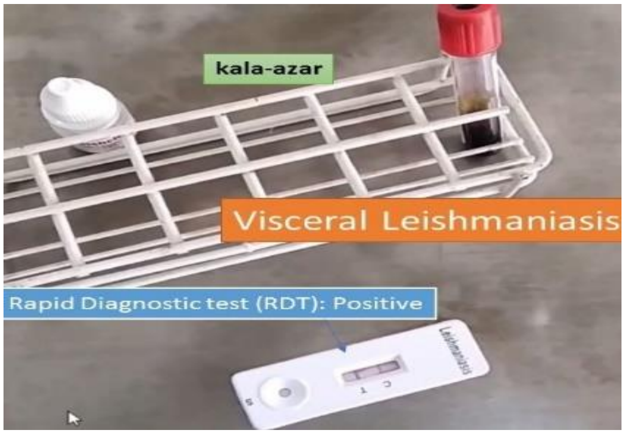
OSCAR
ISO 13485
Kala azar Test
Rapid test for qualitative detection of IgG antibody of Leishmania (Kala azar) in human serum / plasma
rK39 DETECTION
10 T Pack
Kala azar Test
10 Tests
• HIGHLY SENSITIVE & SPECIFIC
• SINGLE STEP AND EASY PROCEDURE



Control
Test
C
T
Leish Leish Leish
SAMPLE
Result: Negative
rK 39 test result for visceral leishmaniasis



K39 test/
Rapid Diagnostic Test of Kala Azar
Leishmaniasis
S
T
C
Positive



kala-azar
Visceral Leishmaniasis
Rapid Diagnostic test (RDT): Positive

10.5.10 RPR (Rapid reagain card test for syphilis)

Materials

- The following are provided in the test kits:

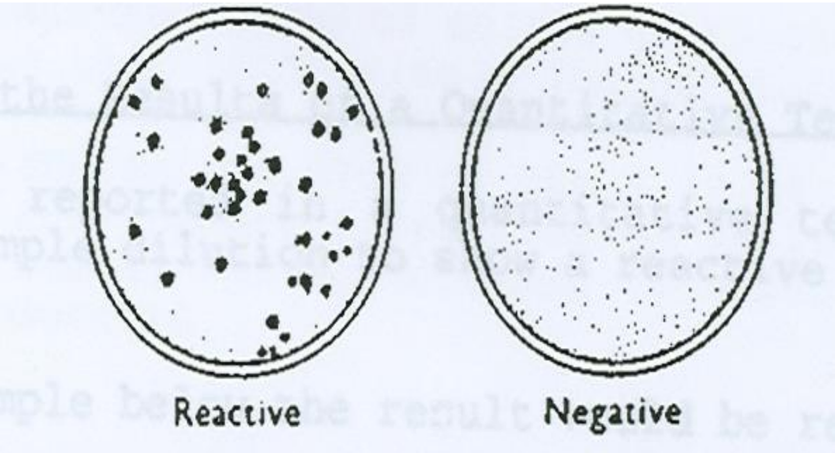
- Reagin antigen suspension
- Reagin positive control serum
- Reagin negative control serum
- Reagin test card
- Dispensing bottle and needle
- Dropper tubes
- Mixing sticks

Procedure

- Let the reagents and specimens warm up to room temperature.
- Dispense one drop of negative control serum on to one circle on the test card using a disposable dropper tube.
- Repeat step two with the positive control serum using a clean dropper tube.
- Dispense on drop of each sample serum or plasma on to one circle on the card using a clean dropper tube for each specimen.
- Spread all the drops to cover the whole area of the circles using the mixing sticks.
- Mix with reagain antigen suspension in the dispensing bottle. Hold the bottle vertically and dispense one drop on to each test sample. Do not mix again.
- Place the card on the rotor for 8 minutes at 100rpm.

Reading the results

- Negative result:
    - The carbon particles remain in an even suspension = Non reactive
- Positive result:
    - The carbon particles clump together = Reactive



10.5.11 VDRL Slide Qualitative Test

Procedure:

- Pipette 0.05ml or 1drop of inactivated serum into one ring of the ringed glass slide.
- Add one-drop (1/60ml) antigen suspension onto each serum.
- Rotate slide for 4 minutes. (If rotated by hand on a flat surface, this movement should roughly circumscribed a 2 inch/5mm diameter circle).
- Tests are read immediately after rotation microscopically with a 10x ocular and a 10x objective.

Reading and reporting of results

- Tests are read microscopically with low power objective at 10x magnification, which appears short rod forms. Aggregation of these particles into large or small clumps is interpreted in degrees of
- **Reporting system**
  - No clumping or very slight roughness: *Non-reactive* ***(NR)***
  - Small clumps: *Weakly reactive* ***(WR)***
  - Medium and large clumps: R*eactive* ***(R)***

10.5.12 ASO latex slide agglutination test

Procedure: (Qualitative slide method)

- Allow each component to reach room temperature.
- Gently shake the latex reagent to disperse the particles.
- Place a drop of undiluted serum on to the circle of the test slide using the disposable pipettes provided.
- Add one drop of the latex reagent next to the drop of serum.
- Spread the latex reagent and serum sample over the entire area of the test circle.
- See for agglutination by tilting the test slid for 2 min.

Interpretation

- Agglutination indicates a positive result which ≥200IU/ml and no agglutination indicates a negative result, which are 200IU/ml provided that the controls have given the expected results.

10.6 Basic microbiological tests

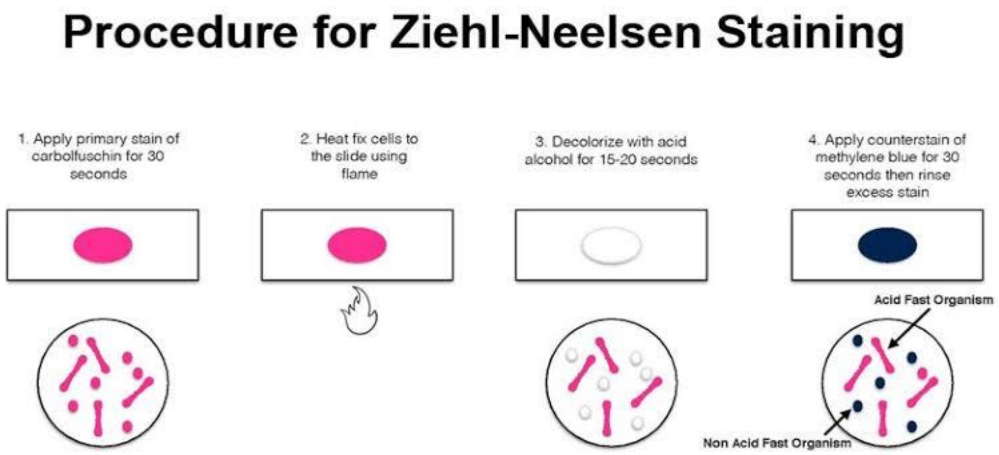
10.6.1 AFB

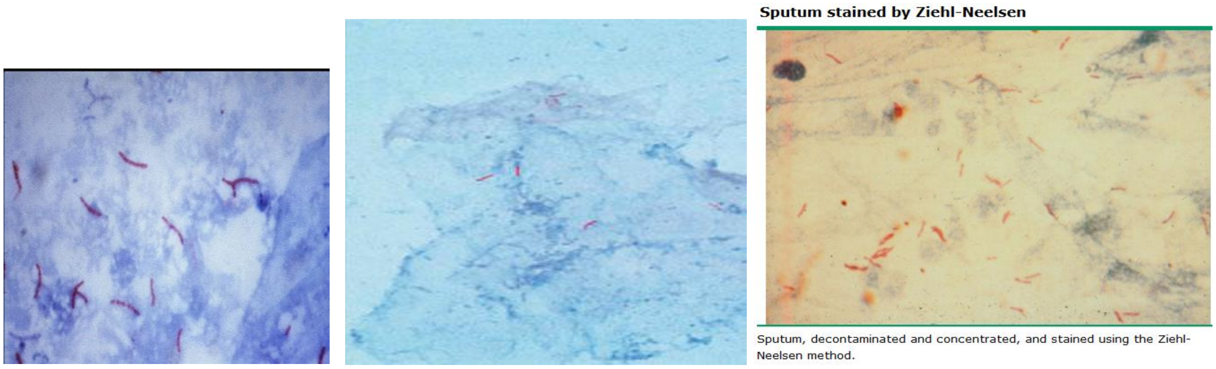
- The detection of acid-fast bacilli (AFB) on microscopic examination of stained sputum smears is the most rapid and inexpensive TB diagnostic tool.
- A serious of **at least 3 single specimens** should be **collected in 8 to 24 hours interval** (with **at least one** specimen obtained **early in the morning**) which should be submitted to the laboratory for AFB smear and mycobacterial culture, although the **diagnosis often can be made with 2 specimens**

  - **Spot - morning - spot examination (currently we are using spot - spot examination only)**
- If pt present with dry cough, use induced sputum with BAL or hypertonic saline method
- Sputum AFB smears are relatively **less sensitive (45 - 80%)** than nucleic acid amplification (NAA) or culture; **approximately 10,000 bacilli per mL are needed for detection of bacteria** in AFB smear using light microscopy.
- AFB sensitivity from Pleural fluid is 10 - 25%

Ziehl-Neelsen staining technique

- The Ziehl-Neelsen staining technique is a differential staining technique that was initially developed by Ziehl and modified later by Neelsen, hence the name Ziehl-Neelsen stain.
- The Mycobacterial cell is difficult to stain by gram staining because they possess a waxy envelope and a special method has to be used.
- Besides being difficult to stain, once it is stained the organism is hard to decolorize.
- Acid-fast bacteria can't be affected by acid alcohol or 20% sulphuric acid, so named as acid fast.
- **Required reagents** → CAM
  - Carbol-fuchsin → primary stain
  - Acid-Alcohol → 20% sulphuric acid as Decolorizer
  - Methylene blue/Malachite green → counterstain
- **Procedure**
  - Prepare the smear from the primary specimen and fix it by passing through the flame and label clearly
  - Place fixed slide on a staining rack and cover each slide with concentrated carbol fuchsin solution.
  - Heat the slide from underneath with sprit lamp until vapor rises (do not boil it) and wait for 3-5 minutes.
  - Wash off the stain with clean water.
  - Cover the smear with 3% acid-alcohol solution until all color is removed (two minutes).
  - Wash off the stain and cover the slide with 1% methylene
  - Blue for one minute.
  - Wash off the stain with clean water and let it air-dry.
  - Examine the smear under the oil immersion objective to look for acid fast bacilli.
- **Results and Interpretation**
  - **Acid-fast bacteria** retain the primary dye, carbol-fuschin, and stain pink **or** Red
  - **Non-acid fast** bacteria take up the methylene blue dye and appear **Dark blue** **or** Blue.
- Applications of Ziehl-Neelsen Staining
  - Used for examination and identification of Mycobacterium species including *M. tuberculosis and M. leprae*.
  - Used to differentiate between acid-fast and non-acid fast bacilli
  - Used for the identification of some fungal species such as Cryptosporidium.


Procedure for Ziehl-Neelsen Staining
1. Apply primary stain of carbolfuschin for 30 seconds
2. Heat fix cells to the slide using flame
3. Decolorize with acid alcohol for 15-20 seconds
4. Apply counterstain of methylene blue for 30 seconds then rinse excess stain
Acid Fast Organism
Non Acid Fast Organism


Sputum stained by Ziehl-Neelsen
Sputum, decontaminated and concentrated, and stained using the Ziehl-Neelsen method.

Pictures; Acid-fast bacillus smear showing *M. tuberculosis* bacilli

How to do an acid fast- staining - Click on the link below and watch the video

https://youtu.be/faB_5STfZH8

10.6.2 Gram stain

- Gram stain is a special stain for the diagnosis of the gram-positive or gram-negative organism in various samples like sputum, pus, CSF, urine, tissue, sample from infected ulcer or wound etc.
- Gram stain divides bacteria in to two physiologic groups, gram positive &gram negative
- The name comes from its inventor, Hans Christian Gram. He published a gram stain method in 1884.
- Indication
  - ✓ To differentiate between gram-positive and gram-negative organisms
  - ✓ To diagnosis the presence of bacteria in sputum, pus, or any other tissue or fluids.

- ✓ CSF gram stain to diagnose bacterial meningitis.
- ✓ It can stain yeast and this needs to be reported.

- **Required reagents** → Come In And Stain
  - Crystal violet → Primary stain
  - Gram's Iodine → mordant
  - Acetone-Alcohol → decolorizer
  - Safranin O → counter stain, secondary stain
- **Procedure** → look at the graphs below
  - Prepare smear from specimen or culture.
  - Allow the smear to air-dry.
  - Rapidly pass slide three times through flame.
  - Cover fixed smear with crystal violet for one minute and wash with tap water.
  - Tip off the water and cover the smear with Gram's iodine for one minute.
  - Wash off iodine solution with tap water.
  - Decolorize with acetone-alcohol for 30 seconds.
    - N.B. A gram-negative bacterium has a high lipid content in outer cell membrane which dissolves in the decolorization process, where the complex will also be washed of, and stain with counter stain (next step)
    - While in Gram-positive bacteria cell membrane remain intact and the stain will not be washed off after alcohol treatment.
  - Wash off the acetone-alcohol with clean water.
  - Cover the smear with safranin for one minute.
    - In gram, positive bacteria counterstain cannot enter so the bacteria are purple.
    - While in gram-negative bacteria safranin can enter and give pink color.
  - Wash off the stain and wipe the back of the slide. Let the
  - smear air-dry.
  - **Observe under microscope and report the result (**Examine the stained smear with oil immersion objective to look for bacteria).
    - **Gram positive bacteria** → retain the primary stain, violet **or** deep purple in color
    - **Gram negative bacteria** → stain with counter stain, appear are pink, magenta color.
    - Yeast cells → Dark purple
    - Nuclei of pus cell → Red
    - Epithelia cells → Pale red

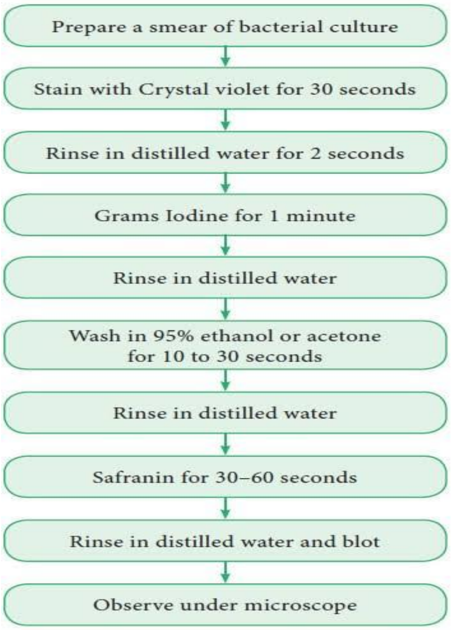
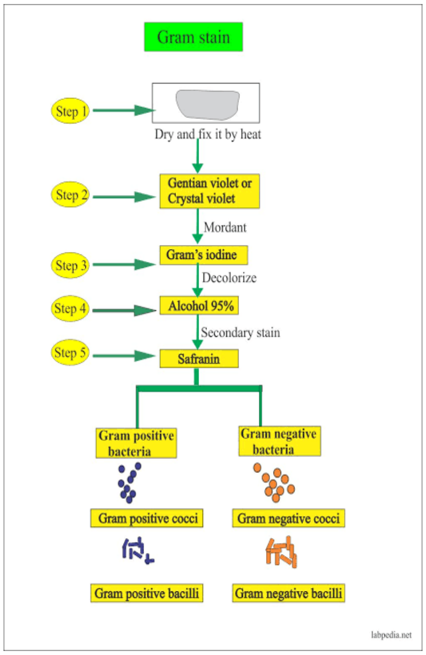
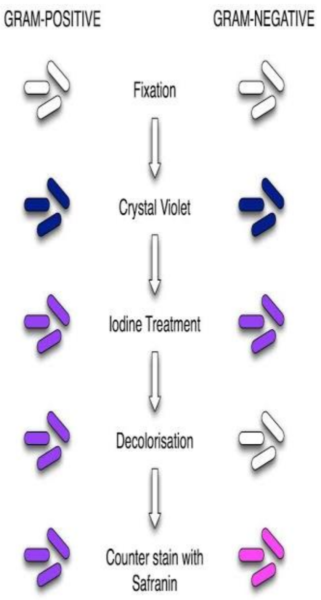
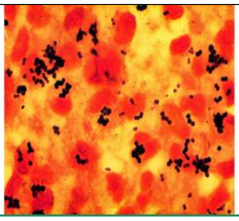
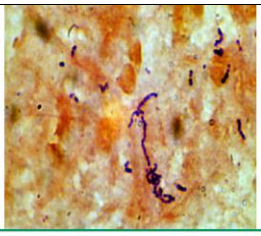
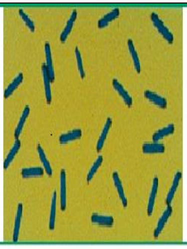
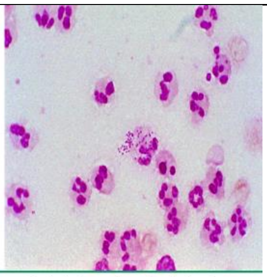
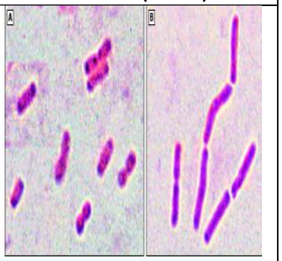

Prepare a smear of bacterial culture
Stain with Crystal violet for 30 seconds
Rinse in distilled water for 2 seconds
Grams Iodine for 1 minute
Rinse in distilled water
Wash in 95% ethanol or acetone for 10 to 30 seconds
Rinse in distilled water
Safranin for 30–60 seconds
Rinse in distilled water and blot
Observe under microscope

Figure 1.10: Steps involved in Gram Staining


Gram stain
Step 1
Dry and fix it by heat
Step 2
Gentian violet or Crystal violet
Mordant
Step 3
Gram's iodine
Decolorize
Step 4
Alcohol 95%
Secondary stain
Step 5
Safranin
Gram positive bacteria
Gram negative bacteria
Gram positive cocci
Gram negative cocci
Gram positive bacilli
Gram negative bacilli
labpedia.net


GRAM-POSITIVE
GRAM-NEGATIVE
Fixation
Crystal Violet
Iodine Treatment
Decolorisation
Counter stain with Safranin

Table; Interpreting gram stain results*

Gram positive			Gram negative (G-ve)	
G +ve cocci		G +ve bacilli (rods)#	G -ve cocci	G -ve bacilli (rods)$
Clusters	Chains			
 Gram stain of sputum (x1000) shows many inflammatory cells and gram-positive cocci in clusters. *Staphylococcus aureus* grew from this specimen on blood agar and tested positive for free coagulase activity.	 Gram stain of an aspirate from a neck abscess (x1000) shows gram-positive cocci in long chains. *Streptococcus pyogenes* (group A *Streptococcus*) grew from this specimen on blood agar and tested negative by catalase.	 Gram-positive rods characteristic of *Clostridium difficile*.	 Gram stain of *Neisseria gonorrhoeae* in urethral exudate.	 (A) Single and pairs. (B) Single, pair, and short chain.

* Look at culture section, below for each bacterial differentiation with examples

[#] Gram +ve bacilli can be large, medium, small or branching

[$] G -ve bacilli can be Medium to long[plump], Medium to long [thin], Short to long [pleomorphic], Tiny, Curved

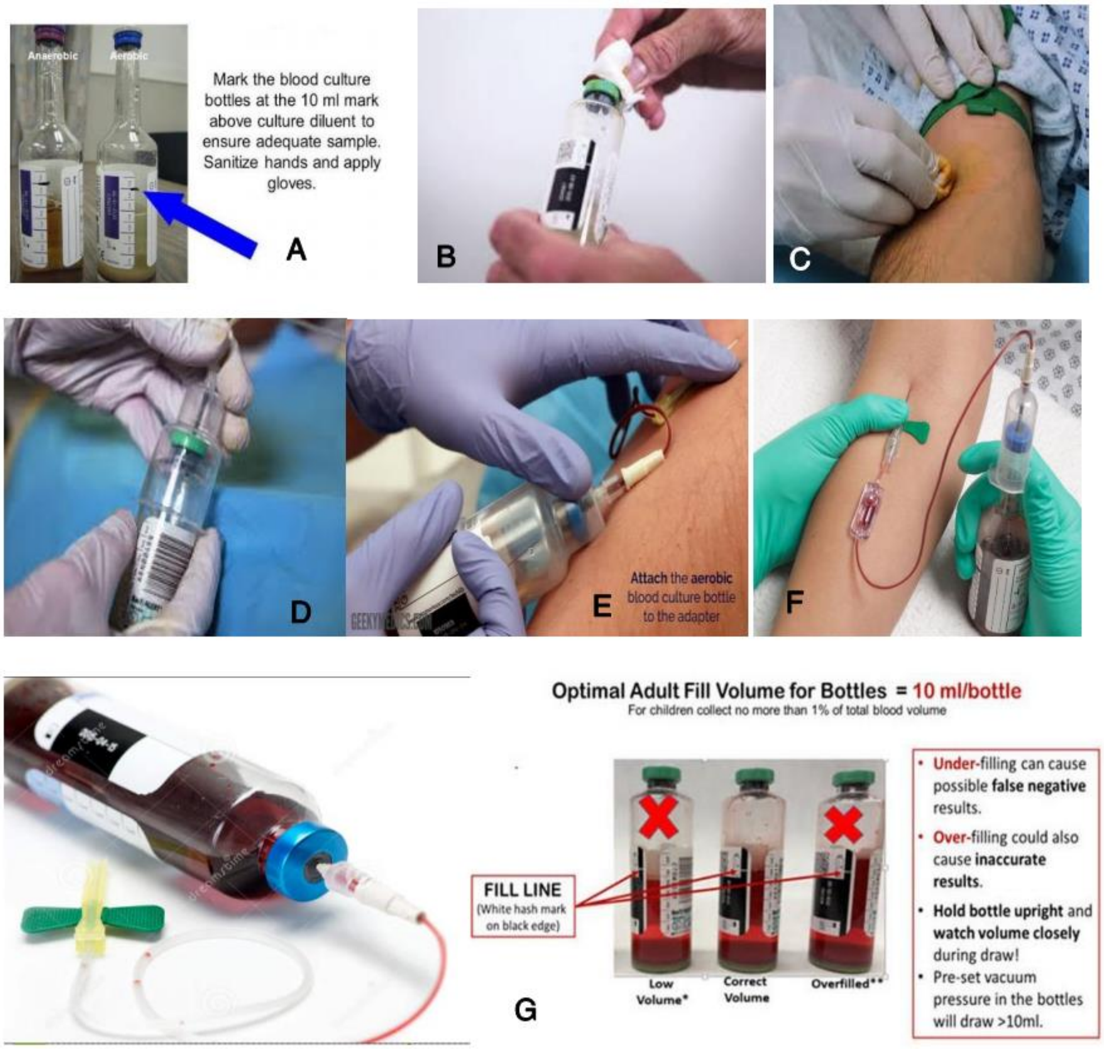
Gram stain - Click on the link below and watch the video
https://youtu.be/ccMvyBcxvJc

10.6.3 Culture & biochemical tests

- Culture is artificial cultivation of microorganisms in the laboratory
- It is important for isolation and identification of microorganisms based on different characteristics such as
  - Colony characteristics
  - Ability to produce pigments
  - Hemolysis
  - Ability to metabolize different nutrients
  - Ability to produce gas

Practical points about sample collection for culture [at bedside]

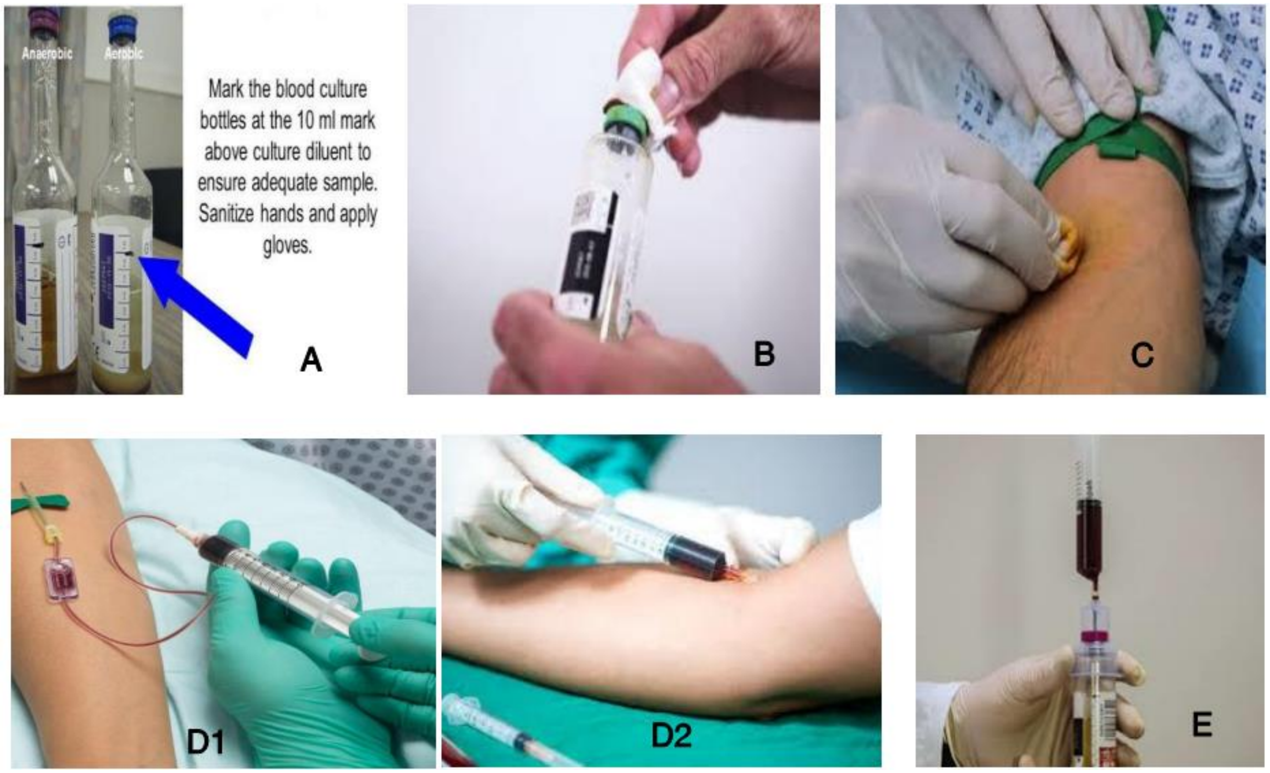
I. Blood culture


Anaerobic
Aerobic
Mark the blood culture bottles at the 10 ml mark above culture diluent to ensure adequate sample. Sanitize hands and apply gloves.
A
B
C
D
Attach the aerobic blood culture bottle to the adapter
E
F
Optimal Adult Fill Volume for Bottles = 10 ml/bottle
For children collect no more than 1% of total blood volume
FILL LINE
(White hash mark on black edge)
Low Volume*
Correct Volume
Overfilled**
Under-filling can cause possible false negative results.
Over-filling could also cause inaccurate results.
Hold bottle upright and watch volume closely during draw!
Pre-set vacuum pressure in the bottles will draw >10ml.
G

Picture; steps of blood culture collection in best setups

A) Mark the blood culture bottle at 10ml to take adequate sample; in addition, bottle should be labeled with patients name, age, sex, date and time of collection, ward

B) Clean the cover area of the bottle
C) Clean and sanitize the sample taking site of the patient
D) Connect bottle to the adapter
E) Insert needle tip of the adapter to patients' vein
F) Hold and wait until adequate sample is taken
G) Check that, correct volume was taken and send sample to lab immediately. Culture result usually expected after 05 days of inoculation in culture media.


Anaerobic
Aerobic
Mark the blood culture bottles at the 10 ml mark above culture diluent to ensure adequate sample. Sanitize hands and apply gloves.
A
B
C
D1
D2
E

Picture; steps of blood culture collection in our set up

A) → Mark the blood culture bottle at 10ml to take adequate sample; in addition, bottle should be labeled with patients name, age, sex, date and time of collection, ward
B) → Clean the cover area of the bottle
C) → Clean and sanitize the sample taking site of the patient with possible aseptic techniques.
D) 1 → connect sterile IV set with 10cc syringe [as shown in the picture], then draw 10ml of blood. This method avoids direct syringe contact with skin, which decreases contamination of sample with skin normal flora

D2 → if D1 is not possible, draw blood directly from vein with 10 cc syringe, keeping possible aseptic techniques to decreases contamination of sample with skin normal flora

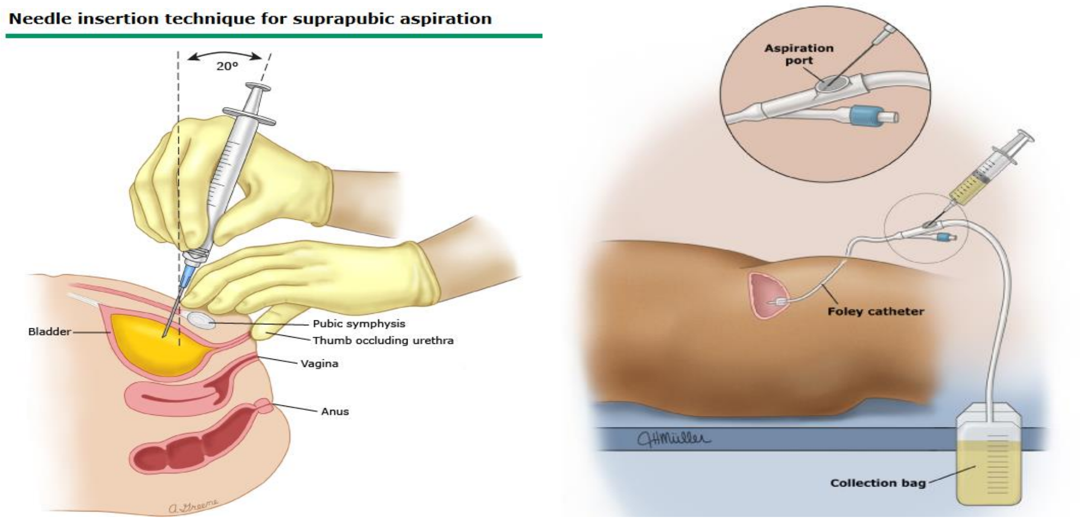
E) Insert needle into a tube containing a culture medium and push the plunger into the barrel to expel contents of the needle onto the side walls of the tube or directly into the liquid phase of the medium (caution !!! → don't open the cap /cover/ of culture bottle at any time of sample collection). Check that, correct volume was taken and send sample to lab immediately after filling the culture request slip. Culture result usually expected after 05 days of inoculation in culture media.

B) Urine culture

- Sample
  - Early morning clean catch mid-stream urine which is collected aseptically by sterile urine cup OR Supra pubic aspirates. For neonates and children urine is collected by sterile plastic bags
  - Foley catheter
  - Urine should be aspirated from the distal end of the catheter with sterile syringe after disinfecting the area (avoid sample taking from the urine bag)
  - Urine specimen should be obtained aseptically without opening the catheter collection junction
- Transport to the laboratory within 01 to 02 hours; if not, keep at 4^0C to avoid multiplication of bacteria in urine
- 24hr urine cultures are not recommended

SPECIMEN CONTAINER
STERILE

Pictures; sterile urine cup for urine culture sample collection

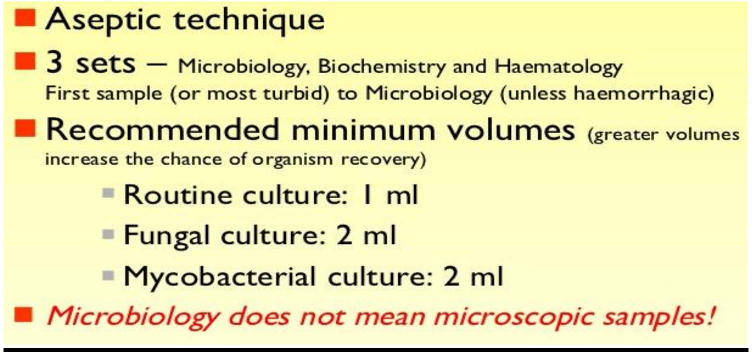


Picture; left) suprapubic aspiration; The needle is inserted one to two centimeters above the pubic symphysis and angled 10 to 20 degrees cephalad. **right) urine culture sample collection from foley catheter system;** Ideally urine samples for culture should be obtained by removing the indwelling catheter and obtaining a midstream specimen. If ongoing catheterization is needed, ideally the catheter should be replaced prior to collecting a urine sample for culture, to avoid culturing bacteria present in the biofilm of the catheter but not in the bladder. Many systems have a "needleless" site that can be cleansed prior to specimen collection. If a sample is being collected without catheter removal, urine should be obtained from the port in the drainage system. For circumstances in which the above approaches are not possible, the culture should be obtained by separating the catheter from the drainage system. Although this approach is associated with some risk of introducing microbes into the closed system, culture results from urine collected from the drainage bag cannot be used to guide treatment.

C) Stool culture

- Stool sample for culture can be collected by a clean, water-tight dry urine free container with a tight lid
- Then place some amount of stool, from the container into sterile culture tube using applicator stick. The stick is available together with sterile tube
- Mix well with the buffer [all sterile tubes of stool culture have buffer inside] inside the tube and level the tube before sending to laboratory.

A) CSF Culture

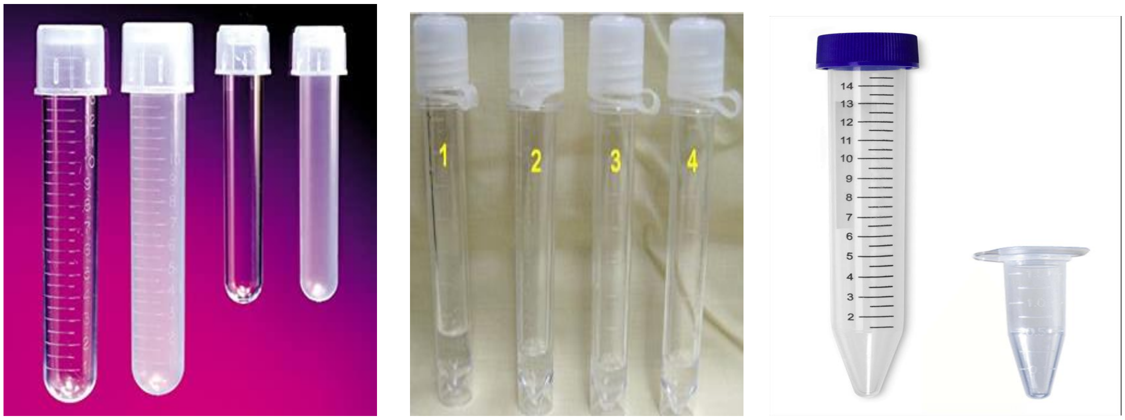


- Aseptic technique
- 3 sets – Microbiology, Biochemistry and Haematology
  First sample (or most turbid) to Microbiology (unless haemorrhagic)
- Recommended minimum volumes (greater volumes increase the chance of organism recovery)
  - Routine culture: 1 ml
  - Fungal culture: 2 ml
  - Mycobacterial culture: 2 ml
- *Microbiology does not mean microscopic samples!*

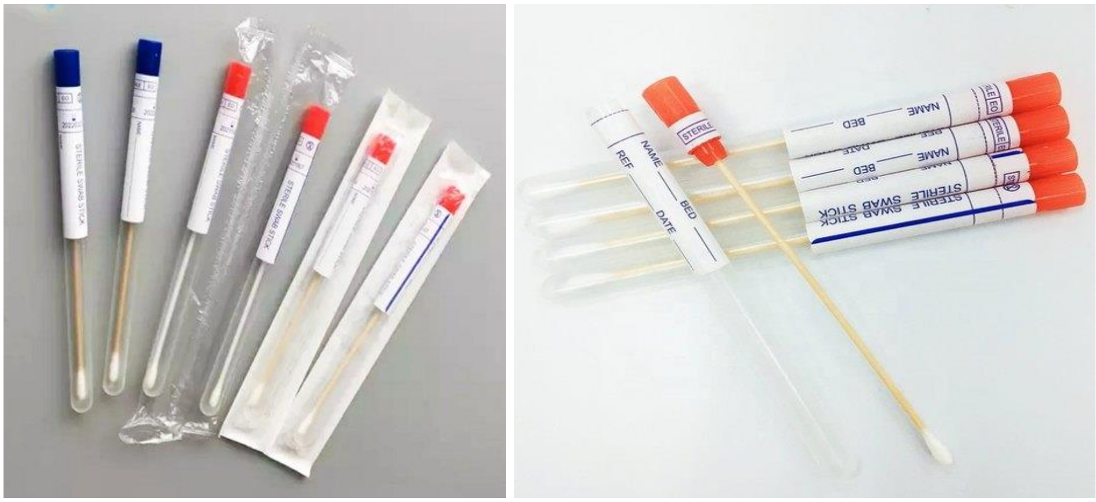
B) Culture from body fluids and wound discharge

❖ Culture from stool, CSF and other body sites collected by sterile tubes

- Sterile Swab is needed [usually available together with sterile tube] to collect stool into sterile tube
- Sterile swab also used to take sample from ulcer and wound discharge



Pictures; sterile culture tubes



Pictures; sterile culture tubes with [cotton] swab stick

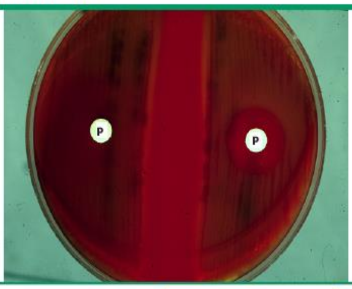
Culture media

A) Blood agar

- Supports the growth of many bacterial pathogens (except *H. influenzae*).
- Blood agar culture plates are also useful for observing hemolysis (the ability of bacterial colonies to break down red blood cells).
- **Types of hemolysis** – The presence of and type of hemolysis is useful for classifying streptococcal species
    - ✓ **Alpha /α/ hemolysis (incomplete or partial hemolysis)** → is caused by bacterial production of hydrogen peroxide, which in turn oxidizes hemoglobin (red) to

methemoglobin (green). *S. pneumoniae* and viridans streptococci display alpha hemolysis

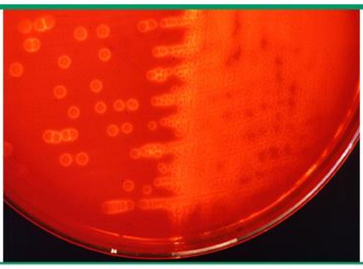
Optochin disk test



Optochin disk test to differentiate alpha-hemolytic (green) streptococci. *Streptococcus pneumoniae* is susceptible to optochin as shown by the zone of inhibition around the disk of the culture on the right. Other alpha-hemolytic streptococci (example on left) are resistant to this compound.

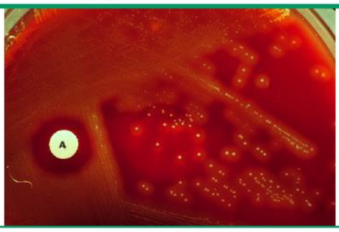
✓ **Beta/β/ hemolysis (complete red cell lysis) →** results in transparency in the normally red agar media. This transparency is typically present around and under the colonies. *Streptococcus pyogenes* and *Listeria* typically display beta hemolysis. Some weakly beta-hemolytic species (eg, *S. agalactiae* and *C. perfringens*) may induce intense beta hemolysis when grown concurrently with *S. aureus*.

Listeria monocytogenes **on blood agar**



The clear areas around each colony of *Listeria monocytogenes* are characteristic small zones of beta hemolysis.

Streptococcus pyogenes **on blood agar**



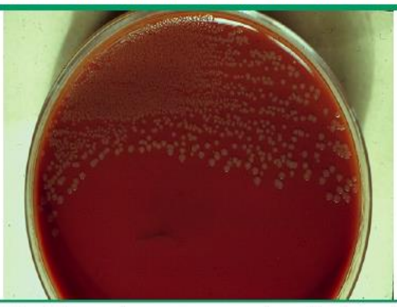
Culture of *Streptococcus pyogenes* on blood agar showing large zones of clear beta-hemolysis around the small colonies. The susceptibility of this organism to bacitracin is demonstrated by the zone of inhibition around the bacitracin-containing disc (A) on the left side of the plate.

✓ **Gamma /γ/ hemolysis (no hemolysis) →** results in no change in the agar color around and under the colony. *Enterococcus faecalis* (formerly group D *Streptococcus*) displays gamma hemolysis.

✓ Hemolytic streptococci are further categorized by Lancefield grouping (see below)

Chocolate agar → named for its brown color

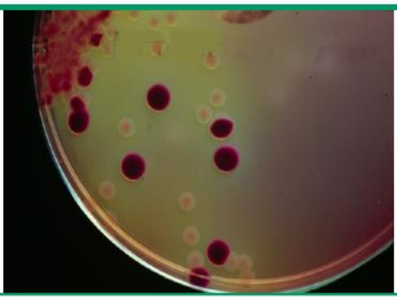
Haemophilus influenzae **on chocolate agar plate**



Haemophilus influenzae does not grow on a sheep blood agar plate but does produce small, translucent colonies on chocolate agar.

MacConkey agar → selective medium designed to detect gram-negative bacteria

MacConkey agar

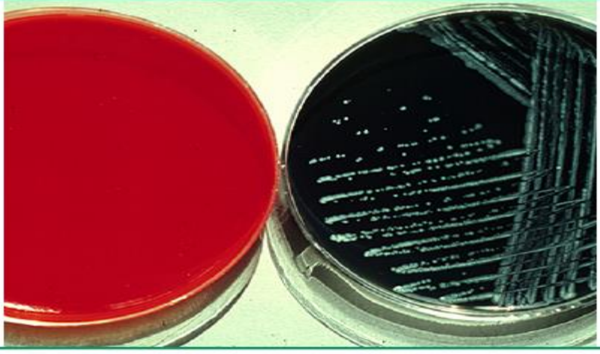


Because of the abundant normal flora present in stool, detection of enteric pathogens requires culture on selective and differential media. MacConkey agar inhibits the growth of gram-positive bacteria and differentiates between gram-negative bacteria that ferment lactose (pink to red colonies on this medium) and those that do not (colorless). Neither *Salmonella* nor *Shigella* can ferment lactose on this medium.

Selective medias

- Helps to detect specific pathogenic organisms growing concurrently with normal colonizing bacteria in specimens collected from nonsterile sites.
- Pathogens that may be identified with selective media include *Bordetella pertussis*, *Salmonella* species, *Shigella* species, *N. gonorrhoeae,* and *Legionella pneumophila*

Legionella on BCYE

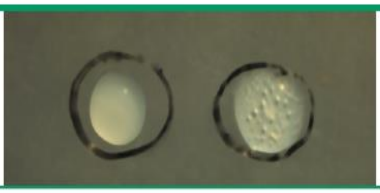


Parallel cultures of *Legionella* on blood (left) and buffered charcoal-yeast extract (BCYE) agar medium (right). *Legionella* only rarely grows on blood agar; it is best isolated on BCYE.

Biochemical tests (Bench tests)

Catalase test → used to distinguish staphylococci (catalase +ve) from streptococci (catalase -ve) and enterococci.

Test for production of catalase



Catalase splits hydrogen peroxide into water and oxygen. The streptococci (left) are catalase negative while organisms such as staphylococci (right) are catalase positive and produce bubbles when mixed with hydrogen peroxide.

Coagulase test → used to differentiate *S. aureus* from other staphylococci (CoNS /S. epidermidis/)

Tube test for free coagulase activity

When *Staphylococcus aureus*, which produces coagulase, is incubated in plasma, a visible fibrin clot is formed (lower tube). Coagulase-negative organisms (top tube) do not form this complex.

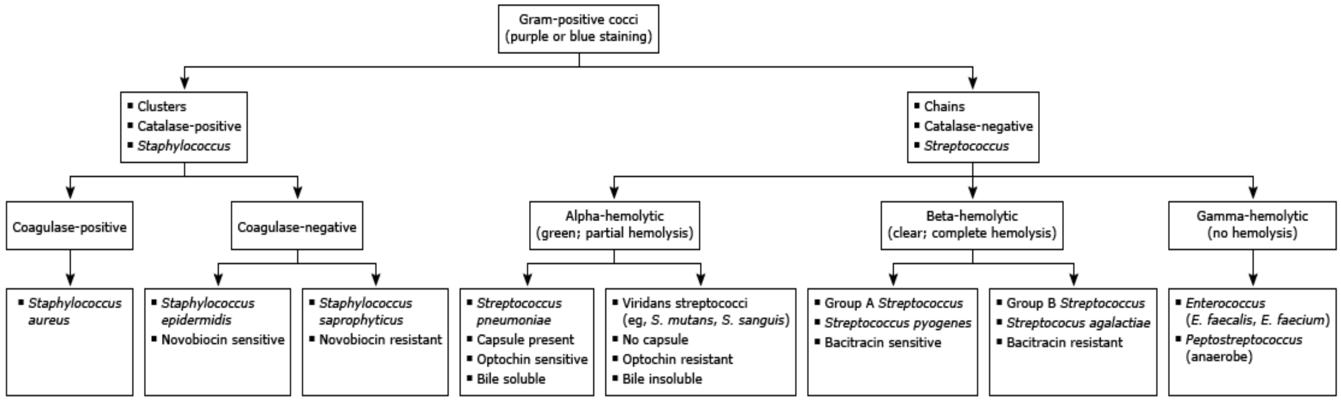
Oxidase test

- Used to differentiate gram-negative bacilli based on their production of certain cytochrome c oxidases.
- A positive result is indicated by a purple color change that is detectable within a few seconds.
- **Oxidase-positive** organisms include → *P. aeruginosa*, *Pasteurella multocida*, *Vibrio,* and *Aeromonas* species.
- Oxidase-negative organisms include → Enterobacteriaceae (such as *E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, *Serratia* spp) and *Acinetobacter* species.

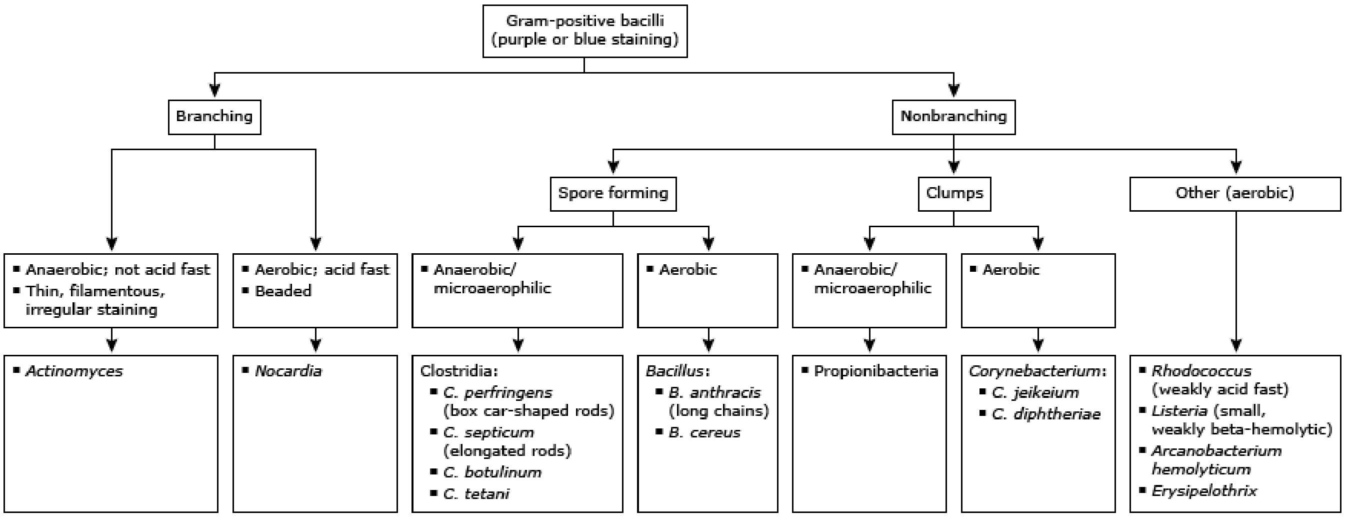
Lancefield grouping

- Lancefield grouping of hemolytic streptococci groups are based on specific carbohydrates in the bacterial cell wall that allow agglutination with particular antisera. Not all streptococci can be grouped; some species such as *S. pneumoniae* do not express Lancefield antigens
- usually used to identify beta-hemolytic streptococci but may also be used to help identify other streptococci and enterococci. For example, *Enterococcus* species are usually group D; *S. anginosus* group are frequently group F but may be groups A, C, or G.

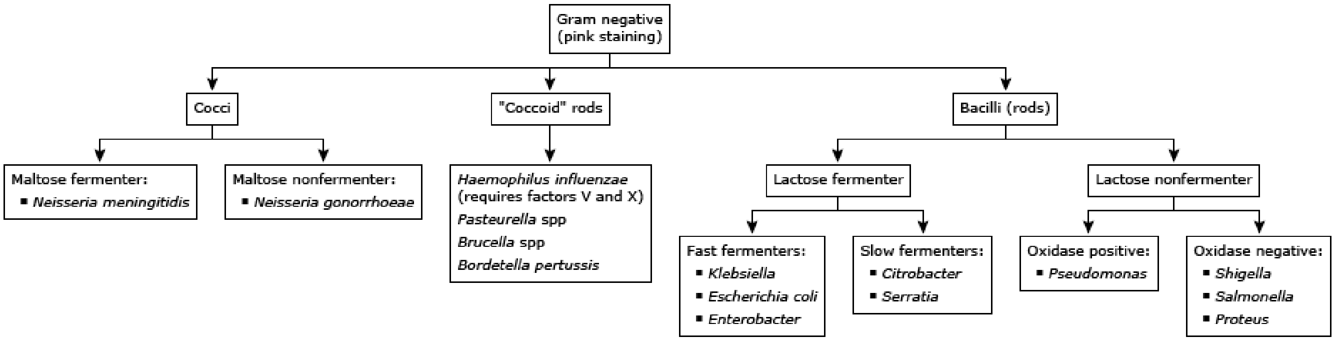
Classification of gram-positive cocci by laboratory features


Gram-positive cocci (purple or blue staining)
▪ Clusters
▪ Catalase-positive
▪ *Staphylococcus*
▪ Chains
▪ Catalase-negative
▪ *Streptococcus*
Coagulase-positive
Coagulase-negative
Alpha-hemolytic (green; partial hemolysis)
Beta-hemolytic (clear; complete hemolysis)
Gamma-hemolytic (no hemolysis)
▪ *Staphylococcus aureus*
▪ *Staphylococcus epidermidis*
▪ Novobiocin sensitive
▪ *Staphylococcus saprophyticus*
▪ Novobiocin resistant
▪ *Streptococcus pneumoniae*
▪ Capsule present
▪ Optochin sensitive
▪ Bile soluble
▪ Viridans streptococci (eg, *S. mutans, S. sanguis*)
▪ No capsule
▪ Optochin resistant
▪ Bile insoluble
▪ Group A *Streptococcus*
▪ *Streptococcus pyogenes*
▪ Bacitracin sensitive
▪ Group B *Streptococcus*
▪ *Streptococcus agalactiae*
▪ Bacitracin resistant
▪ *Enterococcus* (*E. faecalis, E. faecium*)
▪ *Peptostreptococcus* (anaerobe)

Classification of gram-positive bacilli by laboratory features


Gram-positive bacilli (purple or blue staining)
Branching
Nonbranching
Spore forming
Clumps
Other (aerobic)
▪ Anaerobic; not acid fast
▪ Thin, filamentous, irregular staining
▪ Aerobic; acid fast
▪ Beaded
▪ Anaerobic/ microaerophilic
▪ Aerobic
▪ Anaerobic/ microaerophilic
▪ Aerobic
▪ *Actinomyces*
▪ *Nocardia*
Clostridia:
▪ *C. perfringens* (box car-shaped rods)
▪ *C. septicum* (elongated rods)
▪ *C. botulinum*
▪ *C. tetani*
Bacillus:
▪ *B. anthracis* (long chains)
▪ *B. cereus*
▪ Propionibacteria
Corynebacterium:
▪ *C. jeikeium*
▪ *C. diphtheriae*
▪ *Rhodococcus* (weakly acid fast)
▪ *Listeria* (small, weakly beta-hemolytic)
▪ *Arcanobacterium hemolyticum*
▪ *Erysipelothrix*

Classification of gram-negative organisms by laboratory features


Gram negative (pink staining)
Cocci
"Coccoid" rods
Bacilli (rods)
Maltose fermenter:
▪ *Neisseria meningitidis*
Maltose nonfermenter:
▪ *Neisseria gonorrhoeae*
Haemophilus influenzae (requires factors V and X)
Pasteurella spp
Brucella spp
Bordetella pertussis
Lactose fermenter
Lactose nonfermenter
Fast fermenters:
▪ *Klebsiella*
▪ *Escherichia coli*
▪ *Enterobacter*
Slow fermenters:
▪ *Citrobacter*
▪ *Serratia*
Oxidase positive:
▪ *Pseudomonas*
Oxidase negative:
▪ *Shigella*
▪ *Salmonella*
▪ *Proteus*

For antibiotics sensitivity and antibiotic coverage of each bacteria click here → Chapter 7; Basics about rational use of antibiotics

Further reading → UpToDate 2018 (Approach to Gram stain and culture results in the microbiology laboratory, culture section)

Chapter 11; Reference Intervals for Laboratory Tests

Dr. Mulualem. G

Analyte				**SI unit**	**Conventional units**
Hematology					
CBC (Complete blood count)					
Leucocyte with Differential blood count		Alkaline phosphatase (ALP)		0.2–1.6 μkat/L	13–100 μ/L
		WBC		**3.54–9.06 × 10^9/L**	**3.54–9.06 × 10^3/mm3**
	Relative counts:	**Neutrophils**		**0.40–0.70**	**40–70%**
		Bands		**0.0–0.05**	**0–5%**
		Lymphocytes		**0.20–0.50**	**20–50%**
		Monocytes		**0.04–0.08**	**4–8%**
		Eosinophils		**0.0–0.6**	**0–6%**
		Basophils		**0.0–0.02**	**0–2%**
	Absolute counts:	Neutrophils		1.42–6.34 × 10^9/L	1420–6340/mm3
		Bands		0–0.45 × 10^9/L	0–450/mm3
		Lymphocytes		0.71–4.53 × 10^9/L	710–4530/mm3
		Monocytes		0.14–0.72 × 10^9/L	140–720/mm3
		Eosinophils		0–0.54 × 10^9/L	0–540/mm3
		Basophils		0–0.18 × 10^9/L	0–180/mm3
Erythrocyte count		Adult males		4.30–5.60 × 10^9/L	4.30–5.60 × 10^6/mm3
		Adult females		4.00–5.20 × 10^{12}/L	4.00–5.20 × 10^6/mm
Hematocrit		**Adult males**		**0.388–0.464**	**38.8–46.4**
		Adult females		**0.354–0.444**	**35.4–44.4**
Hemoglobin		Plasma		6–50 mg/L	0.6–5.0 mg/dL
		Whole blood:	**Adult males**	**133–162 g/L**	**13.3–16.2 g/dL**
			Adult females	**120–158 g/L**	**12.0–15.8 g/dl**
Mean corpuscular hemoglobin (MCH)				**26.7–31.9 pg/cell**	**26.7–31.9 pg/cell**
Mean corpuscular hemoglobin concentration (MCHC)				**323–359 g/L**	**32.3–35.9 g/dL**
Mean corpuscular hemoglobin of reticulocytes (CH)				24–36 pg	24–36 pg
Mean corpuscular volume (MCV)				**79–93.3 fL**	**79–93.3 μm3**
Mean platelet volume (MPV)				9.00–12.95 fL	9.00–12.95
Platelet count				**165–415 × 109/L**	**165–415 × 103/mm3**
Platelet, mean volume				6.4–11 Fl	6.4–11.0 μm3
Reticulocyte count	Adult males			0.008–0.023 red cells	0.8–2.3% red cells
	Adult females			0.008–0.020 red cells	0.8–2.0% red cells

ESR	**Females**			**0–20 mm/h**	**0–20 mm/h**
	Males			**0–15 mm/h**	**0–15 mm/h**
CRP				<10 mg/L	<10 mg/L
CRP, high sensitivity	Cardiac risk	Low		<1.0 mg/L	<1.0 mg/L
		Average		1.0–3.0 mg/L	1.0–3.0 mg/L
		High		>3.0 mg/L	>3.0 mg/L
Chemistry including Hormonal and chemokine analysis					
Electrolytes	Sodium			136–146 mmol/L	136–146 meq/L
	Potassium			3.5–5.0 mmol/L	3.5–5.0 meq/L
	Chloride			102–109 mmol/L	102–109 meq/L
	Calcium			2.2–2.6 mmol/L	8.7–10.2 mg/dL
	Calcium, ionized			1.12–1.32 mmol/L	4.5–5.3 mg/dL
	Phosphorus, inorganic			0.81–1.4 mmol/L	2.5–4.3 mg/dL
	Magnesium			0.62–0.95 mmol/L	1.5–2.3 mg/dL
Liver enzymes	**Alanine aminotransferase (ALT, SGPT)**			**0.12–0.70 µkat/L**	**7–41 U/L**
	Aspartate aminotransferase (AST, SGOT)			**0.20–0.65 µkat/L**	**12–38 U/L**
	Gamma glutamyl transferase (GGT)			**0.15–0.99 µkat/L**	**9–58 U/L**
	Phosphatase, alkaline (ALP)			**0.56–1.63 µkat/L**	**33–96 U/L**
	ALP, bone	Male		≤20 µg/L	≤20 ng/mL
		Female	Premenopausal	≤14 µg/L	≤14 ng/mL
			Postmenopausal	≤22 µg/L	≤22 ng/mL
LFT	**Albumin**			**40–50 g/L**	**4.0–5.0 mg/dl**
	Protein, total			**67–86 g/L**	**6.7–8.6 g/dL**
	Bilirubin	**Total**		**5.1–22 µmol/L**	**0.3–1.3 mg/dL**
		Direct		**1.7–6.8 µmol/L**	**0.1–0.4 mg/dL**
		Indirect		**3.4–15.2 µmol/L**	**0.2–0.9 mg/dL**
RFT	**Creatinine**	**Female**		**44–80 µmol/L**	**0.5–0.9 mg/dL**
		Male		**53–106 µmol/L**	**0.6–1.2 mg/dL**
	Urea nitrogen (BUN)			**2.5–7.1 mmol/L**	**7–20 mg/dL**
TFT	**TSH (thyrotropin)**			**0.34–4.25 mIU/L**	**0.34–4.25 µIU/mL**
	Thyroxine, free (fT4)			**9.0–16 pmol/L**	**0.7–1.24 ng/dL**
	Thyroxine, total (T4)			**70–151 nmol/L**	**5.4–11.7 µg/Dl**
	Triiodothyronine, free (fT3)			**3.7–6.5 pmol/L**	**2.4–4.2 pg/mL**
	Triiodothyronine, total (T3)			**1.2–2.1 nmol/L**	**77–135 ng/dL**
	Thyroglobulin			13–318 µg/L	1.3–31.8 ng/mL
	Thyrotropin receptor antibody			≤1.75 IU/L	≤1.75 mIU/mL
Calcitonin		Male		0–7.5 ng/L	0–7.5 pg/mL
		Female		0–5.1 ng/L	0–5.1 pg/mL
Lipid profile	**Cholesterol**	**Ranges depend on individual patient factors; see 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol**			
		Total	**Normal**	< 5.17 mmol/L	<200 mg/dL
			Borderline	5.17 - 6.18 mmol/L	200 - 239 mg/dL
			High	≥ 6.21 mmol/L	≥ 240 mg/dL
		HDL	**Normal**	≥ 1.55 mmol/L	≥ 60 mg/dL
			Lower	< 1.03 mmol/L	< 40 mg/dL
		LDL		1.8 - 4.9 mmol/L	70 -190 mg/dL

	Triglycerides (Triglycerides should be measured after fasting for 12 to 14 hours)	**Normal**	**0.34–1.69 mmol/L**	**30–149 mg/dL**
		Mildly elevated	1.7 - 5.6 mmol/L	150- 499 mg/dL
		Moderately elevated	5.6 - 10.0 mmol/L	500 - 886 mg/dL
		Very high	> 10.0 mmol/L	> 886 mg/dL
Coagulation profile	The normal range varies by laboratory and reagent/instrument combination			
	PT (Prothrombin time)		11–13 second	
	aPTT (Activated partial thromboplastin time)		25 - 35 seconds. ➢ **For heparin monitoring**, it is recommended that each laboratory establish the therapeutic range by determining the aPTT range that corresponds **to 0.2 to 0.4 units/mL** by protamine titration or 0.3 to 0.7 anti-factor Xa units/mL.	
	INR (international normalized ratio) INR = $\left[\frac{\textbf{Patient PT}}{\textbf{Control PT}}\right]^{ISI}$ ISI = international sensitivity index		**Therapeutic range 2-3 (**dimensionless**)**	
	TT (thrombin time)		14 to 19 seconds	
	Bleeding time		Bleeding usually stops within 4-8 min	
Troponin I (*99th percentile of a healthy population)*			**Method-dependent**	**Method-dependent**
Troponin T (*99th percentile of a healthy population)*			**0–14 ng/L**	**0–14 ng/L**
Rheumatoid factor			**<15 kIU/L**	**<15 IU/mL**
Uric acid		**Females**	**0.15–0.33 mmol/L**	**2.5–5.6 mg/dL**
		Males	**0.18–0.41 mmol/L**	**3.1–7.0 mg/dL**
Antinuclear antibody (ANA)			**Not applicable**	**Negative at 1:40**
B-type natriuretic peptide (BNP) Age and gender specific:			**<100 ng/L**	**<100 pg/mL**
Creatine kinase (total)		**Females**	**0.66–4.0 µkat/L**	**39–238 U/L**
		Males	**0.87–5.0 µkat/L**	**51–294 U/L**
Creatine kinase-MB		**Mass**	**0.0–5.5 µg/L**	**0.0–5.5 ng/mL**
		Fraction of total activity (by electrophoresis)	**0–0.04**	**0–4.0%**
Anti-thyroglobulin antibody			<40 KIU/mL	<40 IU/mL
Anti-Smith antibody			Not applicable	<1.0 U
Anti-smooth muscle antibody			Not applicable	1.0 U
Adrenocorticotropin (ACTH)			1.3–16.7 pmol/L	6.0–76.0 pg/mL
Erythropoietin			4–27 U/L	4–27 U/L
Ferritin		Female	10–150 µg/L	10–150 ng/mL
		Male	29–248 µg/L	29–248 ng/mL
Iron			7–25 µmol/L	41–141 µg/dL
Iron-binding capacity			45–73 µmol/L	251–406 µg/dL
Chemokines	**Alpha fetoprotein/AFP/ (adult)**		**0–8.5 µg/L**	**0–8.5 ng/ml**
	Prostate-specific antigen (PSA)		**0.0–4.0 µg/L**	**0.0–4.0 ng/mL**
	Prostate-specific antigen, free *With total PSA between 4 and 10 µg/L and when the free PSA is:*		>0.25 decreased risk of prostate cancer. <0.10 increased risk of prostate cancer	>25% decreased risk of prostate cancer <10% increased risk of prostate cancer
	Lactate dehydrogenase (LDH)		**2.0–3.8 µkat/L**	**115–221 U/L**
	CA 125		<35 kU/L	<35 U/mL

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	CA 19-9			<37 kU/L	<37 U/mL
	CA 15-3			<33 kU/L	<33 U/mL
	CA 27-29			0–40 kU/L	0–40 U/mL
	Carcinoembryonic antigen (CEA)	Nonsmokers		0.0–3.0 μg/L	0.0–3.0 ng/mL
		Smokers		0.0–5.0 μg/L	0.0–5.0 ng/mL
FSH	**Female**	**Menstruating**	**Follicular phase**	**3.0–20.0 IU/L**	**3.0–20.0 mIU/mL**
			Ovulatory phase	**9.0–26.0 IU/L**	**9.0–26.0 mIU/mL**
			Luteal phase	**1.0–12.0 IU/L**	**1.0–12.0 mIU/mL**
		Postmenopausal		**18.0–153.0 IU/L**	**18.0–153.0 mIU/mL**
	Male			**1.0–12.0 IU/L**	**1.0–12.0 mIU/mL**
LH	**Female**	**Menstruating**	**Follicular phase**	**2.0–15.0 U/L**	**2.0–15.0 mIU/mL**
			Ovulatory phase	**22.0–105.0 U/L**	**22.0–105.0 mIU/mL**
			Luteal phase	**0.6–19.0 U/L**	**0.6–19.0 mIU/mL**
		Postmenopausal		**16.0–64.0 U/L**	**16.0–64.0 mIU/mL**
	Male			**2.0–12.0 U/L**	**2.0–12.0 mIU/mL**
Serum HCG	Nonpregnant female			<5 IU/L	<5 mIU/mL
	1–2 weeks postconception			9–130 IU/L	9–130 mIU/mL
	2–3 weeks postconception			75–2600 IU/L	75–2600 mIU/mL
	3–4 weeks postconception			850–20,800 IU/L	850–20,800 mIU/mL
	4–5 weeks postconception			4000–100,200 IU/L	4000–100,200 mIU/mL
	5–10 weeks postconception			11,500–289,000 IU/L	11,500–289,000mIU/mL
	10–14 weeks postconception			18,300–137,000 IU/L	18,300–137,000mIU/mL
	Second trimester			1400–53,000 IU/L	1400–53,000 mIU/mL
	Third trimester			940–60,000 IU/L	940–60,000 mIU/mL
Progesterone	Female:	Follicular		<3.18 nmol/L	<1.0 ng/mL
		Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
	Male			<3.18 nmol/L	<1.0 ng/mL
17- Hydroxy progesterone (adult)	Male			<4.17 nmol/L	<139 ng/dl
	Female:	Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
		Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Testosterone, free		Female, adult		10.4–65.9 pmol/L	3–19 pg/mL
		Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,		Female		0.21–2.98 nmol/L	6–86 ng/dL
		Male		9.36–37.10 nmol/L	270–1070 ng/dL
Prolactin		Male		53–360 mg/L	2.5–17 ng/mL
		Female		40–530 mg/L	1.9–25 ng/mL
Lamellar body count (LBC)		Immature		<15,000/μL	15,000–50,000/μL
		Indeterminate		15,000-50,000/μL	15,000-50,000/μL
		Mature		>50,000/μL	>50,000/μL
Lecithin/sphingomyelin (L/S) ratio		Immature		≤1.5	≤1.5
		Transitional		1.5–1.9	1.5–1.9

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	Mature	2.0–2.5 or greater	2.0–2.5 or greater
Cortisol	Fasting, 8 a.m.–12 noon	138–690 nmol/L	5–25 µg/dL
	12 noon–8 p.m.	138–414 nmol/L	5–15 µg/dL
	8 p.m.–8 a.m.	0–276 nmol/L	0–10 µg/dL
Alpha1 antitrypsin (AAT)		1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH3		11–35 µmol/L	19–60 µg/dL
Amylase (method dependent)		0.34–1.6 µkat/L	20–96 U/L
Insulin		14.35–143.5 pmol/L	2–20 µU/mL
Glucagon		40–130 ng/L	40–130 pg/mL
Glucose		**3.6–5.3 mmol/L**	**65–95 mg/dL**
Glucose (fasting)/FBS/	**Normal**	**4.2–5.6 mmol/L**	**75–100 mg/dL**
	Increased risk for diabetes (Impaired Glucose level)	**5.6–6.9 mmol/L**	**100–125 mg/dL**
Diabetes mellitus		**FBS ≥7.0 mmol/L**	**FBS ≥126 mg/dL**
		OGTT ≥11.1 mmol/L	**OGTT ≥200 mg/dL**
		RBS ≥11.1 mmol/L in symptomatic pt	**RBS ≥200 mg/dL in symptomatic pt**
Hemoglobin Alc	**Normal**	**0.04–0.06 Hgb fraction**	**4.0–5.6%**
	Prediabetes	**0.057–0.064 Hgb fraction**	**5.7–6.4%**
	Diabetes mellitus	**HBA1c level ≥ 0.065 Hgb fraction as suggested by the ADA**	**HBA1c level of ≥6.5% as suggested by the ADA**
C peptide		**0.27–1.19 nmol/L**	**0.8–3.5 ng/mL**
Gastrin		<100 ng/L	<100 pg/mL
Growth hormone		0–5 µg/L	0–5 ng/mL
Somatostatin		<25 ng/L	<25 pg/mL
β-Hydroxybutyrate		60–170 µmol/L	0.6–1.8 mg/dL
Ketone (acetone)		Negative	Negative
Lactate	Arterial	0.5–1.6 mmol/L	4.5–14.4 mg/dL
	Venous	0.5–2.2 mmol/L	4.5–19.8 mg/dL
Protein C	Total antigen	0.70–1.40	70–140%
	Functional	0.70–1.30	70–130%
Protein S	Total antigen	0.70–1.40	70–140%
	Functional	0.65–1.40	65–140%
	Free antigen	0.70–1.40	70–140%

U/A (urine analysis)

Sediment	Red blood cells	0–2/high-power field
	White blood cells	0–2/high-power field
	Hyaline casts	0–5/low-power field
	Bacteria	None
	Crystals	
	Bladder cells	
	Squamous cells	
	Tubular cells	
	Broad casts	

	Epithelial cell casts		
	Granular casts		
	Red blood cell casts		
	Waxy casts		
	White cell casts		
pH		5.0–9.0	5.0–9.0
Specific gravity:	After 12-h fluid restriction	>1.025	>1.025
	After 12-h deliberate water intake	≤1.003	≤1.003
Protein		<0.15 g/d	<150 mg/dl (+2 or less)
Protein/creatinine ratio	Male:	15–68 mg/g	15–68 mg/g
	Female:	10–107 mg/g	10–107 mg/g
Microalbumin	Normal	0.0–0.03 g/d	0–30 mg/d
	Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
	Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio	Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
	Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
	Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
Ketone (acetone)		Negative	Negative
Glucose (glucose oxidase method)		0.3–1.7 mmol/d	50–300 mg/dl (+1 or less)
Oxalate	Male	80–500 µmol/d	7–44 mg/d
	Female	45–350 µmol/d	4–31 mg/d
Osmolality		100–800 mosm/kg	100–800 mosm/kg
Phosphate (phosphorus) (varies with intake)		12.9–42.0 mmol/d	400–1300 mg/d
Urea nitrogen		214–607 mmol/d	6–17 g/d
Uric acid (normal diet)		1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)		<30 µmol/d	<6 mg/d
Acidity, titratable		20–40 mmol/d	20–40 meq/d
Glomerular filtration rate (GFR)		>60 mL/min/1.73 m2 (For African Americans, multiply the result by 1.21)	>60 mL/min/1.73 m2 (For African Americans, multiply the result by 1.21)
Arterial blood gas analysis Arterial blood gas analysis			
(HCO3$^-$)		22–30 mmol/L	22–30 meq/L
Pco2 (Sea Level, Fio2 0.21)		4.7–6.0 kPa	35–45 mmHg
Po2 (Sea Level, Fio2 0.21, age related)		8.9–13.8 kPa	67–104 mmHg
Ph		7.35–7.45	7.35–7.45
Carboxyhemoglobin and methemoglobin at pH 7.40 and 37°C		≤0.01	≤1%

Reading assignment

1. Respiratory system
    - Upper respiratory tract infections
    - Acute Bronchitis

2. GI system
    - Hepatocellular carcinoma
    - Diseases of the small intestine (malabsorption syndrome)
    - Dysphagia and esophagitis

3. NS
    - Brain abscess
    - Headache
    - Movement Disorders
    - NMJ disorders
    - Peripheral neuropathies

4. Hematology
    - Hemostasis and bleeding disorders

5. Endocrinology Metabolic disorders
    - Disorders of the thyroid gland
    - Cushing syndrome
    - Adrenal insufficiency
    - Metabolic syndrome
    - Hyper aldosteronism
    - Pheochromocytoma
    - Disorders of pituitary gland
    - Acid base disorders

6. Infectious disease
    - Staphylococcal and Streptococcal Infections
    - Anthrax/ቁርባ/, *Clostridium Difficile* Infection
    - Shigellosis
    - Brucellosis
    - Virology → HSV, Influenza viruses, Ebola virus/ኢቦላ/
    - Viral AFI → Dengue fever/ደንጉ/, Yellow fever/ቢጫ ወባ/, Chikungunya/ችጉንጉንያ/
    - Rabies (የእብድ ውሻ በሽታ)
    - Filariasis, Lymphatic (Elephantiasis)/ዝሆኔ/

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